VOLUME 53 NUMBER 10 OCTOBER 1960

PROCEEDINGS

of the

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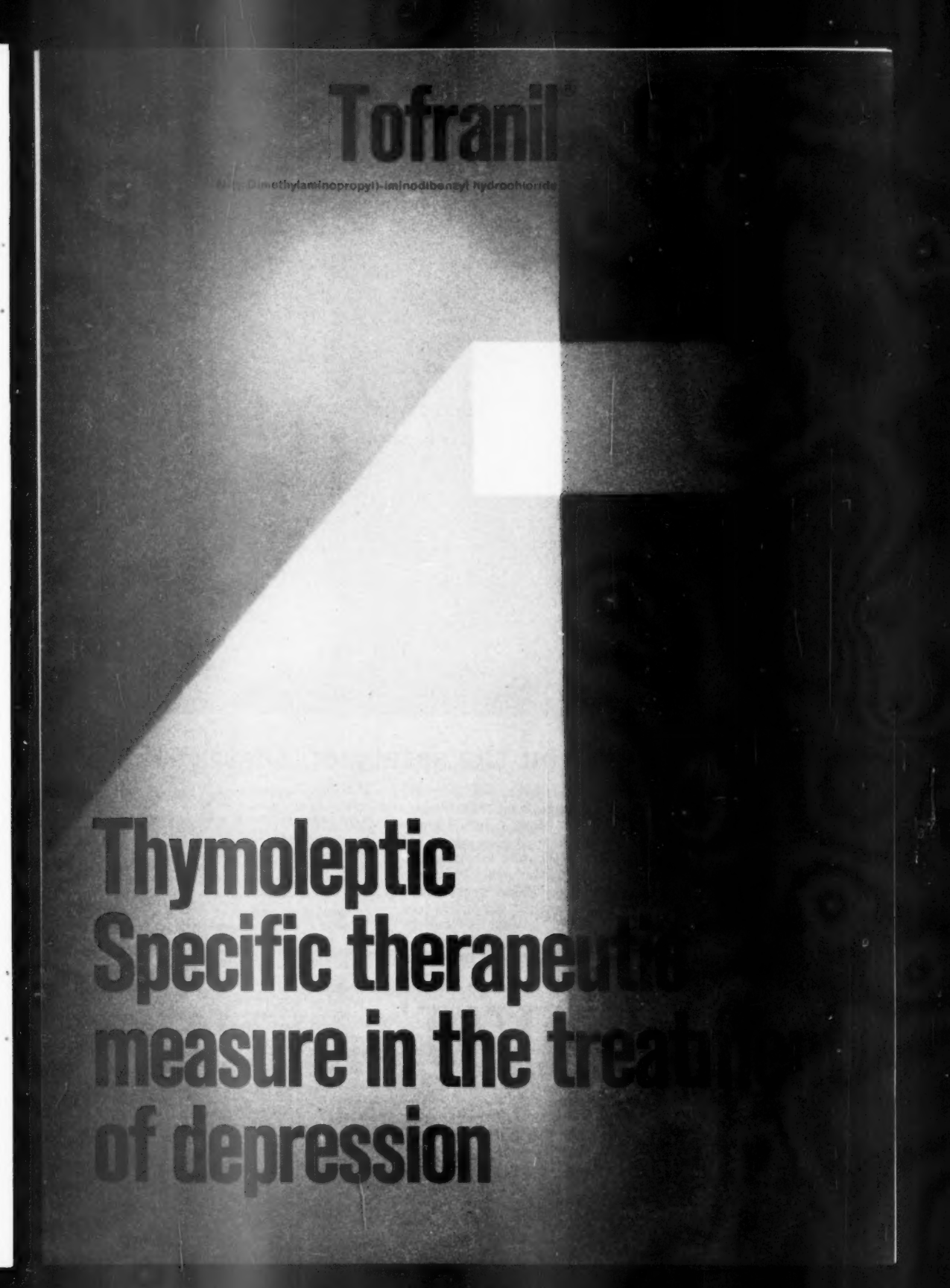
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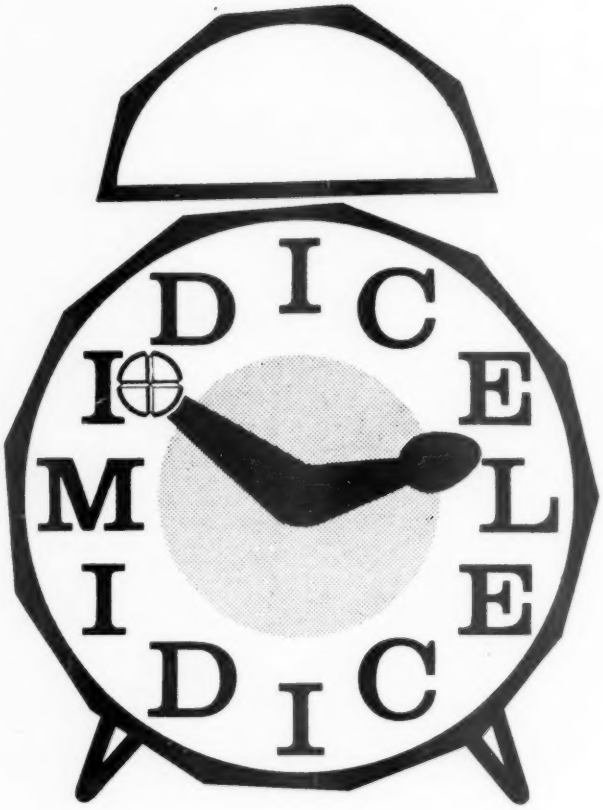

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Section of Urology

President—D. S. POOLE-WILSON, M.Ch., F.R.C.S.

Meeting
October 22, 1959

Occupational Tumours of the Bladder

PRESIDENT'S ADDRESS

By D. S. POOLE-WILSON, M.Ch., F.R.C.S.
Manchester

Introduction

It is now almost sixty-five years since Rehn of Frankfurt-on-Main (1895) first drew attention to the unusual incidence of bladder tumours amongst men employed in the dye-making industry. He described the occurrence of bladder tumours in 3 (and possibly in a fourth) out of 45 workmen, who had been engaged for many years in the manufacture of fuchsin. These men were employed in a workshop where crude fuchsin was produced by the heating together of toluidines, aniline, nitrobenzene and ferric chloride. The conditions of working at this time may be gathered from Rehn's description that "as regards the melting shop on hot days when there is much evaporation of nitrobenzol, aniline and so on, new workmen are often so affected by such urgency of micturition that urine passes involuntarily into their clothes". Rehn concluded that: (1) The fumes which develop during the manufacture of fuchsin lead to disturbances in the urinary system. (2) After years of working in the fuchsin industry tumours of the bladder may occur as a result of the continuous irritation. (3) The injurious effect is mainly due to the inhalation of aniline vapour.

Since that time a vast amount of work has been carried out in the industrial and experimental fields in an endeavour to elucidate the problem of causation and prevention. The clinical aspect of the tumours has been less fully surveyed and so far as I am aware has never been presented to this Section. The following review is based on those cases which have been under the care of Macalpine and myself in Manchester.

Historical Review

Although mauveine—the first coal tar dye—was synthesized by Perkin of London in 1856, the dye manufacturing industry did not flourish for long in England and later became established mainly in Germany and to a lesser extent in Switzerland. It is therefore not surprising that the early records of occupational bladder tumours are almost entirely from German and Swiss sources.

At first Rehn's views were severely criticized, but other similar cases soon appeared and by 1906 Rehn was able to report 33 additional cases collected from seven different factories. Further reports by Leuenberger of Basle (1912) and by Schewin (1920), Curshman (1920), Oppenheimer (1920) and others in Germany left no doubt that bladder tumours were an occupational hazard in the dye manufacturing industry. Many more reports have appeared from Germany culminating in that of Gross (1940). Since 1933 Müller has reviewed the incidence in the Swiss chemical industry and in 1951 published his treatise. He records 161 patients (139 cases of vesical tumour and 22 of hæmorrhagic cystitis).

During and after the First World War dye manufacturing plants were started in other countries and in due course so-called "aniline tumours" began to appear. In England Wignall (1929) and Macalpine (1929) drew attention to this occupational danger. Goldblatt (1947, 1949) reviewed his experiences from two British chemical factories and produced records of 99 cases. Scott (1952, 1959) has also contributed a valuable series of cases. During 1947 the Association of British Chemical Manufacturers instituted a research project, which resulted in the invaluable statistical reports of Case *et al.* (1954).

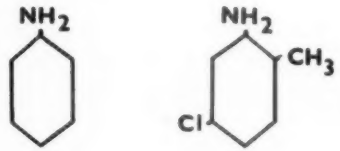
In the United States the first case was recorded by Anderson in 1931 and was quickly followed by the reviews of Ferguson (1934), Gehrman (1934), Gay (1934, 1937), Anderson (1934) and Evans (1937). Maguigan (1950) details nearly 200 cases which had occurred in America. Melick (1958) has recorded 16 cases amongst 71 men manufacturing 4-amino-diphenyl (xenylamine). Series of cases have also been reported from Italy (Di Maio, 1937, 1949), Barsotti and Vigliani (1949, 1952). In France Billiard-Duchesne has described his findings (1949, 1958).

Occupational tumours have also occurred in the manufacture and use of substitution products of alpha- and beta-naphthylamine, which have been used as antioxidants in the rubber industry (Case and Hosker, 1954). Benzidine has also been used in rubber manufacture.

Search for the Carcinogenic Agents

The dye-stuffs manufacturing industry is complex, involving many processes and the handling of many chemicals. This has rendered the search for the bladder carcinogen very difficult. In general all synthetic dyes are derived from coal tar products. Their manufacture may be divided into three main stages: firstly, the production of crude coal tar compounds such as benzene, toluene, xylene, naphthalene and anthracene; secondly the manufacture of intermediate compounds from these chemicals; and thirdly, the manufacture of the dyes from the intermediate products. Vesical tumours are found mainly amongst men employed in the second division and to a lesser extent in the third. There is little or no evidence that handling of the finished dyes induces tumours.

In the past in a dye-stuffs factory many men moved from process to process as occasion required and were seldom continuously on any one plant. This multiplicity of exposure made identification of the carcinogens difficult. The fact that a considerable period of exposure to the carcinogens may be required, and that even then a long latent period may elapse before a tumour appears, has led to further confusion. Many workers may also have left the industry before their tumours develop and their future course may remain unknown. Industrial chemicals may also contain considerable quantities of impurities and at times it is problematic as to which substance is the carcinogen. Furthermore a fair number of intermediate products in a dye-works, although apparently not carcinogenic, are capable of causing considerable vesical irritation and have added to the perplexity. Ortho-



A B

FIG. 1.—A, Aniline. B, 5-chlor-ortho-toluidine, a non-carcinogenic bladder irritant.

toluidine and 5-chlor-ortho-toluidine (Fig. 1B) are particularly irritating and may cause hæmaturia. From amidst all this confusion by the careful analysis of the known works histories of men developing tumours and by animal experiments with the suspected carcinogens the following facts appear to have been established:

Aniline (Fig. 1A).—Although the lesions are still frequently referred to as "aniline tumours" this substance has now been exonerated as a bladder carcinogen. Over the past forty years in no factory manufacturing aniline have tumours been attributable to it. Animal experiments have also been entirely negative. The tumours arising in Rehn's and other early German and Swiss series were probably attributable to naphthylamines, 4-amino-diphenyl (xenylamine) or other closely related compounds arising as impurities during the manufacture of magenta (fuchsin) or to the actual manufacture of magenta itself.

The Carcinogens (Fig. 2)

Beta-naphthylamine, benzidine and 4-amino-diphenyl (xenylamine) have all been shown to be carcinogens or the precursors of carcinogens in the urinary tract in man and animals.

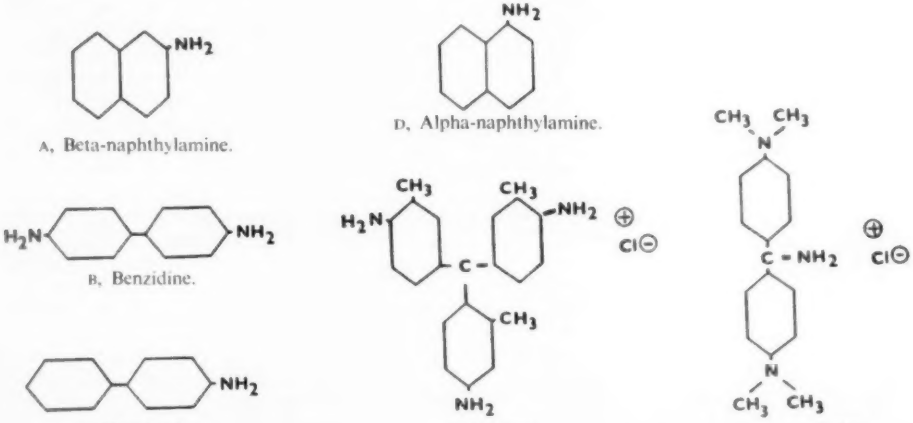


FIG. 2.—The carcinogens.

Beta-naphthylamine.—Clinically Gross (1940), Di Maio (1949), Barsotti and Vigliani (1949, 1952), Scott (1952) and Goldblatt (1947) accepted beta-naphthylamine as a hazard. Experimentally Hueper and Wolfe (1937) and Bonser (1943) obtained bladder tumours in dogs; Bonser *et al.* (1958) have carried out an ingenious series of experiments to test the apparent species differences in the dog, rat, rabbit and mouse to the feeding of beta-naphthylamine. These experiments would appear to indicate that beta-naphthylamine is broken down in the body to metabolites, one of which, 2-amino-l-naphthol, is carcinogenic. It is only in those animals which are capable of breaking beta-naphthylamine down to this metabolite, that tumours can be induced.

Benzidine.—Factory statistics have usually shown a high incidence of vesical tumours amongst men employed in the manufacture and handling of benzidine. Doubts were, however, felt that these men might also have been exposed to beta-naphthylamine. Scott, however, in 1952 definitely established the carcinogenicity of benzidine by describing a series of 30 tumours occurring amongst men exposed to this compound only. Experimentally Spitz *et al.* (1950) obtained bladder tumours in dogs. This finding has been confirmed and many compounds related to amino-diphenyl and diamino-diphenyl have been proved carcinogenic in animals (Walpole *et al.*, 1954; Miller *et al.*, 1956).

Certain homologues and derivatives of benzidine such as tolidine, dichlorbenzidine and dianisidine are used for similar purposes to benzidine but to a much less degree. Their carcinogenicity is not known with certainty; they may be weak carcinogens.

4-*Amino-diphenyl* (*xenylamine*).—Xenylamine—a rubber antioxidant—has never been manufactured in this country. Its potential dangers were recognized and proof of its carcinogenicity in animals established by Walpole *et al.* (1952, 1954). In the U.S.A. the manufacture of xenylamine was begun in 1935. Melick (1958) has described 16 cases of bladder tumour occurring amongst 71 workers (22·5%).

Alpha-naphthylamine.—Workmen manufacturing or using alpha-naphthylamine undoubtedly develop bladder tumours. As manufactured it contains approximately 4% of beta-naphthylamine and this may be the active carcinogen. Evidence is, however, accumulating that alpha-naphthylamine may be a urinary tract carcinogen in its own right.

Magenta and auramine.—The statistical evidence of Case and Pearson (1954) suggests that men engaged in the manufacture of these dyes, and possibly in their handling, may develop vesical tumours. So far it has been impossible to determine whether the hazard can be attributed to the intermediates, impurities or the finished dye (Scott and Williams, 1957*b*).

The Early Diagnosis of Tumours

Occupational tumours of the bladder present no specific signs or symptoms: hæmaturia is the most common heralding sign but by the time of its appearance a tumour may already have reached a considerable size. The invasive and more malignant tumours tend to be relatively silent in their onset and may at first only declare themselves by mild cystitis and faint transient hæmaturia. By the time of investigation they may have extensively permeated or even have penetrated the bladder wall. Amongst a works population, who have been exposed to carcinogens and are thus known to be at risk, there is therefore a great need for a means of early tumour detection. Three methods have been tried as screening measures: (1) Microscopic examination of the urine for red blood cells. (2) Routine cystoscopy. (3) Cytological diagnosis.

Microscopic Examination of the Urine

Oppenheimer (1920) recommended regular microscopic examination of the urine for red blood cells as a means of detecting bladder tumours in men exposed to carcinogens. Since 1934 such regular examinations have been applied in several British dye-stuffs factories. The unstained centrifuged deposits of specimens of urine from men in hazardous processes are microscopically examined at monthly intervals for red and white blood cells. The presence of large numbers or the persistence of small numbers of red blood cells in the urine of a man who had a sufficient exposure to carcinogens is almost invariably regarded as an indication for cystoscopy.

Several factors, however, tend to render the test somewhat inaccurate. Hæmaturia is not specific for bladder tumours and gross or minute quantities of blood may appear in the urine as the result of many diseases. Acute hæmorrhagic cystitis may also be a manifestation of the absorption of certain chemicals such as toluidines or 5-chlor-2-toluidine, which are often made and used in dye-stuffs factories. Red blood cells may also be found in the urine of some apparently healthy individuals. Scott, examining candidates for employment in a dye-works, found that 6·2% of the applicants had microscopic hæmaturia of undetermined origin (more than 6–8 red blood cells per low power field on microscopy of a centrifuged deposit).

Despite the possible disadvantages many pre-symptomatic diagnoses have been made by the

wet smear technique. Scott (1959) has reported that during the eleven years from 1940 to 1950 at one factory 40 men were found to be suffering from bladder tumours. The urine of all had been regularly examined by the wet smear technique. In 16 the presence of red blood cells, observed only on microscopy of the urine, was the sole indication of a tumour. In 12 instances small numbers of red cells, considered to be insufficient in quantity to warrant advising cystoscopy, were present before gross hæmaturia or other symptoms appeared. In the remaining 12 no blood cells were seen before the onset of symptoms. The technique therefore detected an asymptomatic tumour in 16 instances but failed in the remaining 24.

Routine Cystoscopy

Annual routine cystoscopy of all exposed workers was first instituted in the United States (Gehrman, 1934; Wolfe, 1937; Evans, 1937) and was later adopted in other countries (Di Maio, 1949; Barsotti and Vigliani, 1949; Billiard-Duchesne, 1949; Müller, 1951). Many tumours, particularly at the first screening of a works population, have been discovered in this way and if accurately and regularly carried out the examination is undoubtedly an additional safeguard. It appears, however, to be extremely doubtful whether all workmen continue to submit to the examination. In Great Britain routine cystoscopy has never been practised. Even in the gentlest hands the examination is irksome and it has been felt that the many cystoscopies with negative findings may give a false sense of security and lead to refusal of examination at a time when it may be most necessary.

Cytodiagnosis

About 1945 Papanicolaou, who had achieved considerable success in the diagnosis of cancer of the vagina, cervix and uterus by the examination of vaginal smears, turned his attention to the possibility of diagnosing malignant neoplasms of the urinary tract by smears prepared from urinary sediments. The urine for the examination is mixed immediately after collection with an equal quantity of 95% industrial alcohol to prevent cellular disintegration and is then stained by a special technique.

The interpretation of the smears is difficult. The diagnosis is based on the appearance of isolated, or preferably groups of, exfoliated cells. Unfortunately there is no single criterion of malignancy. Papanicolaou bases his classification on structural modifications of the cells and their nuclei and on changes in the inter-relationship of cells as shown in cell clusters and tissue fragments. He records his findings in the following classes: (1) Absence of atypical or abnormal cells. (2) Atypical cytology but no evidence of malignancy. (3) Cytology suggestive but not conclusive of malignancy. (4) Cytology strongly suggestive of malignancy. (5) Cytology conclusive for malignancy.

Classes 1 and 2 are regarded as negative, 3 as suspicious and 4 and 5 as positive.

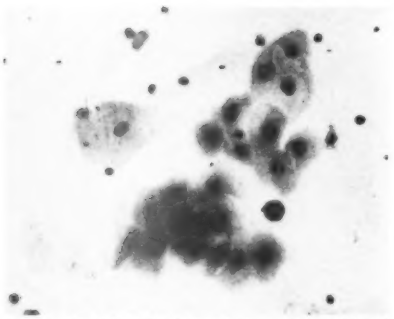
In 1951 the Papanicolaou smear technique was introduced as a screening measure into three large British dye-stuffs factories. From two of these most of the author's patients are drawn. The smear results and the findings of any subsequent cystoscopic examinations were carefully correlated. Crabbe (1952) published a preliminary report. A more comprehensive survey was issued in 1956 by Crabbe *et al.* and a further report by Scott and Williams in 1957(*a*). Table I is produced by courtesy of Scott and Williams and shows the results over a period of seven years of screening approximately 2,000 men who had been engaged in the manufacture or use of bladder carcinogens and another 2,000 whose exposure had been indirect or small. The urine of the most heavily exposed men was examined monthly and of others at three- to four-monthly intervals. Wet smears and Papanicolaou stained smears were examined. As a result of these investigations 108 men were referred for cystoscopy—80 with positive cytological smears and 28, whose smears were negative, on account of erythrocytes in their urine or other symptoms. Cystoscopic investigation revealed 77 patients with bladder tumours. Of these men 70 had positive Papanicolaou smears before they were investigated—32 of these had sufficient erythrocytes in their urine (or in a few cases symptoms) to warrant cystoscopy but 38 had no indication other than the smear findings to show that a tumour was present.

TABLE I.—PAPANICOLAOU TEST RESULTS
(Scott and Williams, 1957*a*)

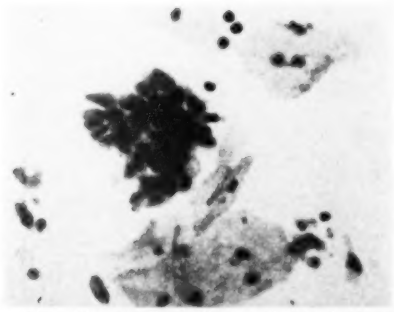
The cystoscopic findings compared with the Papanicolaou smear results in 108 men sent for examination on account of positive Papanicolaou smears or the presence of blood cells in their urine

Cystoscopic finding	Papanicolaou test		Total
	Positive	Negative	
Tumour present ..	70	7	77
No tumour found	10	21	31
Total	80	28	108

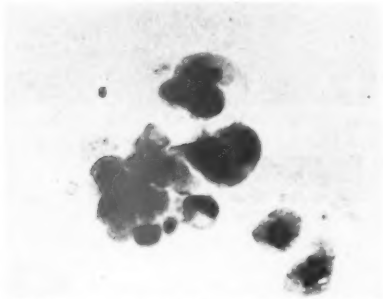
In 31 men no tumour was found on cystoscopy. Of these 21 had negative smears but were examined because they had symptoms or erythrocytes in their urine. 10 men had positive smears and were apparently false positive results —4 had renal calculi, 1 a stricture and another severe burns, 2 of the remaining 4 showed cystoscopic appearances suggestive of early



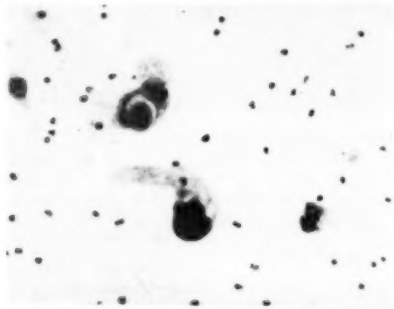
A, Normal epithelial cells and pus cells. ×270. The proportion of cytoplasm to nucleus is normal. The nuclei do not stain deeply.



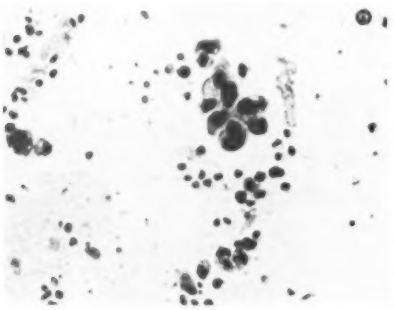
B, Transitional cell papilloma. Normal squamous cells and pus cells are also present. ×330. The cells are clustered. The cytoplasm is reduced. The nuclei are large and stain deeply.



C, Malignant cells—class V. ×440. Cells irregular in shape and size. Vacuoles. Large nuclei, unequal in size and shape, stain deeply. The presence of a tumour was diagnosed on this film. Cystoscopy showed a papillary carcinoma. A biopsy confirmed the diagnosis.



D, Malignant cells—Class V. ×220. The film shows two curious cells with the characteristics of malignancy. Cystoscopy revealed a solid papilloma. Biopsy confirmed the diagnosis of carcinoma.



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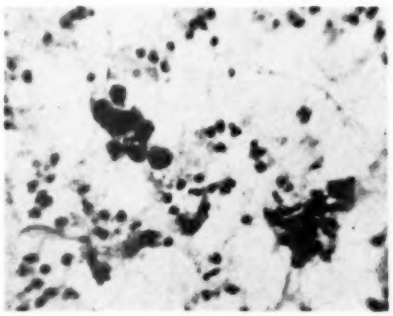

F

E, Malignant cells (Class IV). ×240. Investigation at this time failed to reveal a tumour. The smears continued to be positive. F, Made nine months later again showing tumour cells (Class IV) and pus cells. ×270. A further urinary investigation revealed a tumour in the left renal pelvis. A left nephro-ureterectomy was performed (15.1.57) and the presence of a transitional cell carcinoma confirmed. The patient died of phthisis eleven months later. A post-mortem showed no tumour in the bladder.

FIG. 3.—Papanicolaou smears.

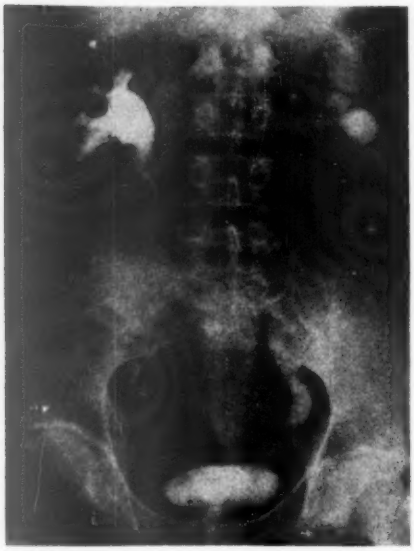

FIG. 4A.—Retrograde pyelogram (1954). Right kidney shows filling defects of the lowest group of calyces and also of the lowest calyx of the uppermost group. The left renal pelvis and calyces are dilated but smooth in contour. The ureter is dilated to within 3 cm of the bladder, where it appears markedly narrowed.

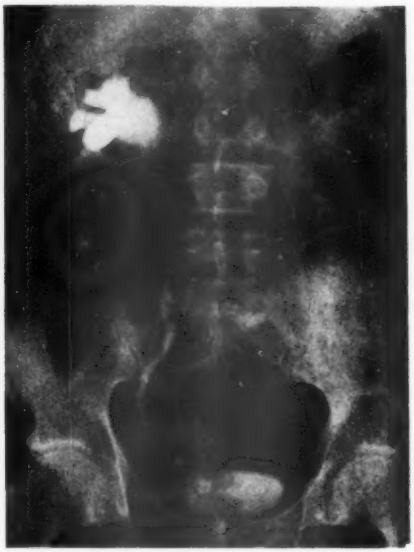

FIG. 4B.—Right retrograde pyelogram (29.4.55). The filling defects of the renal pelvis and calyces have advanced. The outline of an apparent papilloma is visible in the ureter at the level of the sacro-iliac joint. The ureter lower down is irregular.

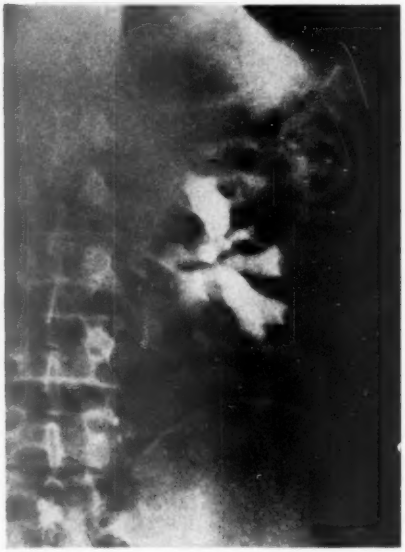

FIG. 4C.—Intravenous pyelogram showing the improvement in the left kidney following the resection of the lower end of the ureter.

FIG. 5.—Specimen of right kidney and ureter removed at operatian showing papillomata of the renal pelvis and ureter.

FIGS. 4 and 5 (*Case I*).—Papillomata of the right renal pelvis and each ureter.

tumour formation and in 2 no abnormality has as yet been detected.

It was hoped that the Papanicolaou technique might provide a useful means of surveillance following treatment of a tumour. Table II

TABLE II
(Scott and Williams, 1957*a*)
A comparison of the Papanicolaou smear results with the findings of 225 review cystoscopies carried out on 47 men, who had been treated for bladder tumour

Papanicolaou smear result	Cystoscopy			
	Negative	Suspicious	Positive	Total
Negative ..	83	10	20	113
Suspicious ..	19	20	4	43
Positive ..	27	27	15	69
Total	129	57	39	225

shows a comparison of the Papanicolaou smear results with the findings of 225 review cystoscopies carried out on 47 men, who had been treated for bladder tumours. Of 129 review cystoscopies in which no tumour was found only 83 of the urines yielded a negative smear. Again of 39 cystoscopies at which a tumour was definitely recognized the urine of 20 gave negative smears. The explanation of these erratic findings is not clear. It must, however, be stressed that the Papanicolaou smear, whilst most useful as a primary screening measure, cannot be relied upon for post-treatment reviews.

THE PRESENT SERIES OF PATIENTS

The present series consists of 182 patients, who have been found to be suffering from occupational tumours of the urinary tract. Of these 180 suffered primarily from bladder tumours; in one case a renal and in another a ureteric lesion was unaccompanied by any bladder lesion.

The majority of these patients have been referred by the Medical Officers of two large factories engaged in the chemical and dye-making industry, but some who had left their former employment have been found in hospital practice and the occupational nature of their lesion has been established from their history and its subsequent confirmation at the factory concerned. 4 patients have been traced to a third small factory which is principally engaged in the manufacture of magenta.

Causative agents.—The exposures to the compounds accepted as industrial bladder carcinogens were: benzidine 43 cases, alpha-naphthylamine 19, beta-naphthylamine 20, mixed contacts (many in contact with beta-naphthylamine) 85, manufacture of magenta 4, and others (including some magenta cases) 11 cases.

Incidence.—The chief incidence has occurred amongst men actively engaged in the manufacture of the carcinogens and to a slightly less degree amongst those using them in the manufacture of dyes or other compounds. Their work classification is: staff men 9, foremen 2, manufacturers 89, users 59, others 23. Although their exposure is less, staff men and foremen have not escaped. There is also an incidence amongst men coming more indirectly into contact with the carcinogens—chemical engineers, plant cleaners, plumbers and even a laundryman, who had handled contaminated clothing.

Period of exposure and latent period.—The amount of contact with a carcinogen necessary to induce tumour formation is difficult to ascertain as it depends on the nature of the carcinogen as well as on the period and intensity of exposure. Estimates are usually based on the period of exposure, which is reckoned as the length of time during which a worker has been engaged on a hazardous process.

The period elapsing between the first exposure and the appearance of a tumour is known as the latent or induction period. When a tumour arises during the period of exposure to the carcinogens, the period of exposure and the latent period are the same. The appearance of the tumour may, however, be delayed and occur long after the man has left the industry. In such instances the latent period is much longer than the period of exposure. Table III shows the latent periods in this series.

TABLE III.—THE LATENT PERIOD

Average age on entry to the industry ..	29 years
Average age at onset of tumour ..	50 years
Average latent period	20¼ years
Longest latent period	41 years
Shortest latent period	3 years

The clinical investigation.—When a man is referred to the Urological Clinic, a full clinical examination, X-ray investigations and cystoscopy are first carried out in the outpatient department. If cystoscopy reveals a vesical tumour the patient is admitted to hospital for a further cystoscopy under general anæsthesia, biopsy of the tumour and a careful bimanual pelvic examination. When the tumour appears suitable for perurethral resection or diathermy the treatment is carried out at this examination. Otherwise the biopsy findings are obtained and the appropriate treatment then determined. It must be remembered that these men, having lived in contact with workmates who have suffered and died from bladder tumours, are fully aware of the implications of a positive finding and therefore require very careful and gentle handling. The following history of a man who worked alongside his mates for the greater part of the eleven years during which he was under treatment, illustrates the possible future envisaged by these men when a tumour is diagnosed:

Case I.—J. E. B., maintenance engineer foreman.
Joined the company in 1928 at 25 years of age

From 1928 to 1945 was exposed to alpha-naphthylamine. In 1945 he developed hæmaturia, and cystoscopy revealed a papilloma in his bladder. In addition he occasionally passed small calculi. At this time he refused treatment.

In 1947 he was again reviewed. Large multiple papillomata were present in the bladder. For these he was given a course of deep X-ray therapy. A calculus was also present in his right kidney. The papillomata regressed but during the following year mossy papillomata in the region of the left ureteric orifice were diathermized. The calculus was also removed from his right kidney.

From 1948 to 1954 recurrent papillomata formed in his bladder and prostatic urethra and were diathermized. The renal tract was also kept under review. Towards the end of 1954 it became evident that papilloma formation was present in the right renal pelvis and ureter and that dilatation of the left renal pelvis and ureter was occurring owing to obstruction of the lower end of the ureter by a papilloma (Fig. 4). The patient was at first reluctant to have any further operative treatment but finally wished that everything possible should be done to prolong his life. After much consideration a right nephro-ureterectomy was performed on 18.5.55 (Fig. 5). 28.9.55: The lower 5 cm of the left ureter were resected and the ureter re-anastomosed to the bladder. Section of tissue from the right kidney and ureter and from the left ureter showed transitional cell papillomata. The patient made a good recovery. Cystoscopy (14.11.55) showed a very scarred and somewhat contracted bladder but no positive evidence of tumour. His frequency gradually increased and he subsequently started to wear a urinal. During August 1956 he had a convulsion whilst at work and was again admitted to hospital. He finally died on 5.9.56. Post-mortem examination revealed a diffuse carcinomatous infiltration of the bladder wall. Secondary deposits were present in the para-aortic glands. Tumour cells were found in the suprarenal glands and their pericapsular lymphatics. Gross pyelonephritis was present in the remaining left kidney.

Cystoscopic findings.—Occupational tumours of the bladder show no special characteristics to distinguish them from spontaneous tumours. In character they may range from the delicately fronded papilloma to the deeply infiltrating carcinoma. There does, however, appear to be a tendency to increased multiplicity and to an unusual incidence of accompanying tumours in the renal pelvis, calyces and ureter (*see* Renal and Ureteric Tumours, p. 810). The appearance of further tumours at new sites is perhaps also more troublesome than in the case of tumours of spontaneous origin. On account of the careful screening of workmen and especially since the advent of the Papanicolaou technique, the tumours tend to be seen at an earlier stage of development than amongst the general population; indeed amongst men still employed in the industry it is now rare to find an advanced tumour at the first cystoscopy.

Gay (1934, 1937) has described congestive lesions consisting of punctate ecchymoses or fine telangiectasia, which are thought to be precursors of tumour formation. Epithelial hyperplasia has also been noted. In the past I have been sceptical of these findings (Poole-Wilson, 1953). Amongst these men there does, however, seem to be an increased incidence of localized congestive lesions or areas of epithelial hyperplasia, but these areas do not necessarily develop into tumours and may appear and disappear. Biopsy of such areas has shown erosion of epithelium with inflammatory cell infiltration and some fibrosis. Their significance is not really understood but they do appear to indicate an unstable mucosa and possible future trouble. Somewhat similar lesions have been seen in experimental animals; McDonald and Lund (1954) noted equivalent findings in their experiments with the implantation of beta-naphthylamine induced tumours.

Primary diagnosis.—At the completion of the initial investigations of 180 bladder tumours, 102 (56·6%) were regarded as simple papillomata. 78 (43·3%) were classified as carcinomata.

The incidence of papillomata appears higher than might have been expected, but a good many papillomata were diagnosed in the days before cystoscopic biopsy examinations were carried out, and some early carcinomata may have been included in this group. Over recent years it has been our aim to carry out a biopsy in every patient. From the pathological aspect, however, there is often difficulty in deciding which tumours are true simple papillomata and which should be regarded as early carcinomata. In this series we have included amongst the benign or transitional cell papillomata those tumours which show a minor degree of cellular polymorphism yet insufficient to warrant regarding them as definite carcinomata. (These tumours are now placed in a special category of simple benign transitional cell papillomata marked "suspect".) The result of this grading is perhaps shown in the fact that of the 102 cases of papillomata, 22 have shown malignant changes either at the same site or elsewhere in the bladder, at a later date.

Treatment

The primary treatment carried out on these patients has varied a little over the years but in general conforms to the following pattern. The benign papillomata and some early papillary carcinomata have been treated by perurethral diathermy or resection. Localized carcinomata which were of suitable size have been treated by open diathermy destruction and interstitial irradiation. The more extensive carcinomata have been subjected to deep X-ray therapy.

Open diathermy destruction of multiple papillomata, partial cystectomy and total cystectomy had been carried out in a few cases. The numbers treated by each method are shown in Table IV.

TABLE IV.—THE PRIMARY TREATMENT OF BLADDER TUMOURS

Perurethral diathermy	108
Interstitial irradiation	31
Deep X-ray therapy	21
Open diathermy, partial and total cystectomy	17
No treatment	3
	180

Perurethral Diathermy Destruction

Cystodiathermy was used in 108 patients as a primary form of treatment.

TABLE V.—PERURETHRAL DIATHERMY

Total number of cases	108
Five-year survival: 65 out of 74 possible survivors	88%

The 88% five-year survival rate appears fairly satisfactory but by no means indicates the full story. Of the 65 survivors 13 died later from vesical tumour; in 5 the tumour reappeared in the bladder over thirteen years after the original onset. 5 other patients later died from natural causes and were apparently tumour free. There are 45 patients, who have survived periods ranging from five to twenty-one years, and who still remain tumour free. 2 further survivors are known to have vesical recurrences.

The survey of these patients leaves no doubt that many benign papillomata and early papillary carcinomata may be controlled by perurethral diathermy. The figures, however, give no indication of the amount of cystoscopic investigation and treatment entailed. The course of the patient may be extremely variable. In some, after primary destruction of the tumour a trouble-free course ensues. In others there may be a period during which recurrent papillomata appear and require regular diathermy treatment. Eventually after a year or two recurrences may cease and the patient have many years of freedom. It is, however, never safe to regard these patients as cured and to dismiss them from care. In a considerable number recurrences or new tumours have appeared after five or more years of complete freedom. Such tumours may once more respond to perurethral treatment. In others these late tumours may gradually get out of control and apparently undergo carcinomatous changes.

In another group of cases recurrent papillomata will continue to appear at varying sites in the bladder and repeated diathermy treatment may be required to hold them in check. In such men it is, of course, essential to make absolutely certain that no renal or ureteric lesion is present.

In other instances, although the amount of tumour on inspection may not appear great, the bladder mucosa may show indefinitely outlined areas of red and apparently thickened mucosa. The appearances suggest that epithelial hyperplasia is present and that the mucosa is in an unstable state. Biopsy examination of these areas may fail to show tumour. These cases present a very dangerous problem because transition to an extensive invasive carcinoma may occur and progress at an extremely rapid pace. In some of these patients the subsequent course has shown that, despite control by biopsy, treatment has persistently lagged behind the progress of the disease. In such instances a decision to use more radical treatment such as deep X-ray therapy should not be too long delayed.

Although treatment may be started by perurethral diathermy the subsequent progress of the case may determine a change of treatment. In the present series, of the 108 cases who were started initially on this line of treatment 18 subsequently required treatment by other means.

Interstitial Irradiation

When the whole bladder mucosa must be regarded as a potential tumour site, interstitial irradiation may appear to be an unsatisfactory form of treatment. It must also be remembered that once a tumour-lethal dose of irradiation has been given to any part of the bladder it is not possible at a later date to carry out any further irradiation. The selection of patients for interstitial irradiation therefore requires great care. As has been previously mentioned, in a proportion of these occupational bladder tumours a localized carcinoma develops and the remainder of the bladder appears to remain free of tumour formation. In 31 such patients interstitial irradiation has been carried out as a primary treatment, with a five-year survival rate of 63% (17 out of 27 possible survivors).

This treatment has been reserved for definite carcinomatous lesions usually of Stage A or B. In some of the earlier cases Stage C lesions were implanted. The 63% five-year survival rate would seem to show that this method of treatment has proved its usefulness. I would, however, reiterate that if there is any suggestion of multiplicity of tumours it should not be used.

Interstitial irradiation has also been used as a secondary method of treatment for localized carcinomata that were primarily treated by perurethral diathermy. There have been 5 cases in this series with a five-year survival rate of 80%.

Deep X-ray Therapy

Deep X-ray therapy has been used as an initial form of treatment on 18 patients (2 palliation only). Of these 16 were suffering from

extensive or multiple carcinomata and 2 from severe multiple papillomatosis. Of the 18 patients 14 qualified for a five-year survival review and 6 or 43% were found to be living. Three of these survivors died at a later date from recurrent bladder tumour. In 4 of the patients who died, the bladder at the time of death appeared to be free from tumour but pelvic secondaries were present.

Deep X-ray was used as a secondary form of treatment in 10 instances. There were only 2 five-year survivals of 7 possible (28%).

Other Forms of Irradiation Therapy

Contact therapy was used on one of the earlier patients. He survived seven years but ultimately died of his tumour. In 2 patients the bladder has been irradiated by a central cobalt source—1 died at three years, the other is a four-year survival.

Radiation from a central source of cobalt has been employed once as a secondary form of treatment.

Renal and Ureteric Tumours

Amongst this series of occupational bladder tumours there has been a considerable incidence of accompanying tumours arising in the renal pelvis and ureter. The first 2 cases were recognized and described by Macalpine (1947). In 1 of these patients the lesion was unilateral, in the other bilateral renal tumours were present. Since then 14 further cases have been identified including 1 in which the tumours were again bilateral. Thus amongst 180 patients suffering from occupational bladder tumours 8·8% also developed renal or ureteric lesions (Table VI).

Table VI.—Renal and Ureteric Tumours
(Total number of patients with occupational tumours of the urinary tract—182)

Renal or ureteric tumour preceded by bladder lesions (2 bilateral)	16 (8·8%)
Renal or ureteric tumour without bladder lesions	2
Total	18 (9·9%)

2 patients have also been found, in 1 of whom a renal and in the other a ureteric lesion were unaccompanied by any bladder manifestation. An attack of painless hæmaturia led to a full investigation in the one instance, whilst the finding of tumour cells in routine Papanicolaou smears was the only indicative sign in the other.

From these findings it is evident that an investigation of men who have been exposed to urinary tract carcinogens must always include a full survey of the upper urinary tract. If intravenous pyelography fails to yield detailed pictures of the renal pelves, calyces and ureters, retrograde pyelograms and ureterograms should be made. The renal or ureteric lesion, however, commonly appears long after a bladder lesion has been found and treated. In fact it is probable that the lengthening of life resulting from early and adequate treatment of the vesical lesion may be the reason for the apparently increasing incidence of renal and ureteric tumours. Persistent recurrent vesical papillomatosis, hæmaturia which cannot be accounted for by a bladder lesion, and renal discomfort are symptoms which indicate the need for a further review of the upper urinary tract.

In 17 of these 18 men the upper urinary tract lesion was identified during life; the remaining renal tumour was found at post-mortem in a patient who had died from an advanced carcinoma of the bladder.

The tumour was confined to the renal pelvis in 13 patients (in 1 a tumour was also present on the other side); in 3 the renal pelvis and ureter were affected (in 1 of these a tumour was present in the other ureter); 2 patients presented ureteric lesions only. No patients presented any certain evidence of previous renal or ureteric stasis. 13 of the 20 lesions were on the left side and 7 on the right. Pathological examination showed that 10 were simple transitional cell papillomata; the remaining 10 showed carcinomatous changes.

The bladder tumours present in 16 of these patients varied considerably in type. In 4 an invasive carcinoma was present. In the remainder the lesion was primarily of a papillomatous nature.

In some this papilloma formation has been a pronounced feature and scattered groups of apparently small benign papillomata have been diathermized on many occasions. If such a state of affairs exists a search should immediately be made for a renal lesion. In this respect the following 2 cases are of interest. In the first the persistent appearance of small benign vesical papillomata ceased following the removal of a kidney containing a simple transitional cell papilloma and would support the view that the vesical papillomata were seedlings. In the second case the removal of a renal lesion made no alteration to the periodic appearance of bladder papillomata.

Case II.—E. M.

In May 1943, when aged 43, seven years after his first exposure to beta-naphthylamine this workman developed hæmaturia. There had been no previous symptoms and routine tests at the factory for blood cells had been negative. Cystoscopy (J. B. Macalpine, 31.5.43) revealed a small bunch of sessile papillomata well above the right ureteric orifice. There was no evidence of infiltration. The papillomata were destroyed by perurethral diathermy. Intravenous pyelography revealed no abnormalities.

From 1943 regular cystoscopic reviews revealed no sign of recurrence until March 1948, when two small

papillomata were noted above the left ureteric orifice, another at the internal meatus and one within the prostatic urethra. Despite careful perurethral diathermy treatment recurrent crops of papillomata kept appearing over the next nine years. During the summer of 1957 he noticed a trace of blood in his urine on one occasion and during the following month complained of some pain in his left loin. Intravenous pyelography revealed a normal right renal pelvis, calyces and ureter. The left kidney was silent. Cystoscopy (3.9.57) showed no papillomata in the bladder or urethra; a faint trace of blood was noted coming from the left ureter. A ureteric catheter ran up this ureter easily for 15 cm and was then obstructed. Pyelogram fluid also failed to run further up the ureter.

10.9.57: Left nephro-ureterectomy. The renal pelvis appeared distended and the ureter dilated to 1 cm in diameter down to a point at the pelvic brim where it became normal in calibre.

FIG. 6 (*Case II*).—Benign papillomata of the renal pelvis and ureter.

Examination of the removed specimen showed some pelvic and calyceal hydronephrosis. In the renal pelvis just above the pelvi-ureteric junction there was a benign type papilloma measuring 2·5 cm in diameter. Half-way down the ureter there was an occluding mass of papillomata about 2 cm in length. Above this mass the ureter was dilated but normal below it (Fig. 6).

Since his operation regular cystoscopic reviews have shown no further recurrences in the bladder. This man is at present apparently free of tumour sixteen years after the original onset of his trouble.

Case III.—J. T. S.

In March 1926, when aged 20, this man entered the dye manufacturing industry. He worked on the manufacture of alpha- and beta-naphthylamine until 1944, when he was referred to hospital on account of cystitis and hæmaturia. Previous routine urine tests for red blood cells had been negative.

Cystoscopy (J. B. Macalpine, 26.6.44) revealed an apparently simple papilloma in the vault of the bladder with a few smaller papillomata just below it. There was no evidence of infiltration. The tumours were destroyed by perurethral diathermy.

Regular review cystoscopies revealed from time to time recurrent papillomata in the bladder and posterior urethra (16.11.46, 17.11.48, 9.4.49, 3.1.51, 24.4.51 and 9.7.51). Occasional hæmaturia was noted during the autumn of 1952. Cystoscopy (27.10.52) revealed no vesical tumour. Intravenous pyelography showed a small calculus in the lowest calyx of the left kidney.

Cystoscopy (27.1.53) showed fronds just median to the left ureteric orifice. These were destroyed with diathermy and bilateral retrograde pyelograms were made. The right kidney and ureter appeared normal. The left pyelogram confirmed the presence of a small calculus in the lowest calyx. The pelvis and upper calyces appeared incompletely filled and deformed. The appearance suggested a tumour of the renal pelvis.

2.2.53: Left nephro-ureterectomy. The mucosa of the upper half of the renal pelvis and of the uppermost calyces was covered with transitional cell papillomata.

Review cystoscopies (25.1.54, 4.10.54) showed recurrent papillomata. During February 1956 some tiny clots were noticed in the urine. Cystoscopy (27.2.56 and 17.9.56) revealed no recurrences in the bladder. A right pyelogram and ureterogram were normal. May 1957: A small papilloma was destroyed at the site of the removed left ureteric orifice. Biopsy showed a simple transitional cell papilloma. During 1958 no recurrences were noted but cystoscopy on 20.2.59 revealed a papilloma (1·5 cm diameter) in the vault of the bladder. A biopsy of this tumour showed a transitional cell papilloma with moderate cellular polymorphism and fairly numerous mitotic divisions.

Treatment

12 patients were treated by nephro-ureterectomy. In one the lower end of the other ureter was later excised on account of papilloma formation. A nephrectomy alone was carried out on one patient. In another a proposed nephro-ureterectomy had to be abandoned on account of the extent of the tumour. 3 patients were too ill for any operative treatment—1 patient suffered from uræmia due to extensive bilateral renal tumours; 2 patients were dying from extensive vesical tumours. In one of these patients post-mortem examination confirmed the presence of a papillary carcinoma in the left renal pelvis but also revealed that a suspected chest secondary was a primary oat cell carcinoma of the right lung.

Urethral Lesions

Vesical papillomata may be accompanied by small and apparently subsidiary lesions arising in the posterior urethra and more rarely in the anterior urethra (Ashworth, 1956). These growths are frequently regarded as seedlings and it has been suggested that urethral instrumentation facilitates their implantation. In the present series a considerable number of such papillomata have been noted in the posterior urethra and to a much lesser extent in the anterior urethra. They have usually responded to perurethral diathermy.

In the following patient malignant changes supervened:

Case IV.—C. B.

During January 1936, when aged 28, this man commenced working in contact with alpha- and beta-naphthylamine. Twelve years later he was referred to Salford Royal Hospital as microscopic hæmaturia had been detected on routine urine investigation. Cystoscopy (18.7.48) revealed a solid papilloma above the right ureteric orifice and a small flat papilloma at 11.0 o'clock on the urethral margin. The papillomata were destroyed with diathermy.

Over the next two years further rather solid papillomata, occurring at various sites in the bladder, were destroyed by perurethral diathermy. Cystoscopy (28.11.50) showed a rather solid tumour on the trigone. Biopsy revealed a poorly differentiated transitional cell carcinoma. A course of deep X-ray therapy was given at the Christie Hospital (25.6.51–27.7.51, 6,000 rads on the 4 MV linear accelerator). The patient subsequently remained clear of tumour until July 1954 when cystoscopy revealed papillomata in the prostatic urethra and at intervals along the bulbous urethra. Biopsy showed a transitional cell tumour with a moderate number of dividing cells. The tumours were treated with diathermy but were proved recurrent and were never completely eradicated. During January 1955 further tumour formation appeared in the bladder. Total removal of the bladder and urethra was advised but refused. The urethra subsequently became grossly thickened from the base of the prostate to the distal portion of the bulb. The patient was finally admitted to hospital with acute retention and early peri-urethral extravasation and died shortly afterwards. Post-mortem examination revealed a carcinoma of the bladder invading the left pelvic wall. Carcinomatous deposits were present in the urethra and had produced a peri-urethral abscess.

One patient in whom the bladder lesion is quiescent has recently developed a carcinoma of the anterior urethra, which appears to be a primary growth:

Case V.—J. C.

This man entered the dye manufacturing industry when 26 years of age and came into contact with alpha- and beta-naphthylamine. After a latent period of twenty-nine years he was investigated on account of an attack of hæmaturia. Cystoscopy (8.1.52) revealed a papilliferous tumour in the vault of the bladder. It measured 2–3 cm in diameter and had a broad base. Biopsy revealed a transitional cell tumour showing nuclear gigantism, hyperchromatism and frequent mitoses. It was classified as a papillary carcinoma. The tumour was destroyed by perurethral diathermy.

During November 1954 and again during August 1955 and April 1956 small papillomata were observed at cystoscopy and destroyed by diathermy. The original tumour site remained free from trouble.

The bladder subsequently remained free from tumour. At cystoscopy (10.2.59) it was noted that the urethra close to the external meatus was a little narrow but no tumour was found in the bladder or urethra. During July 1959 this man complained of difficulty in passing urine and noticed a swelling in his left groin. Examination revealed a carcinoma of the penile urethra with secondary deposits in the left inguinal glands.

28.7.59: Partial amputation of the penis and block dissection of the left iliac glands. The specimen showed a tumour apparently arising from the urethra and invading the corpora cavernosa penis. Microscopy revealed an anaplastic carcinoma, which was squamous in parts and in several areas had an adeno-carcinomatous pattern. Comparison of the histology with the vesical tumour removed in 1952 did not suggest that this urethral tumour was metastatic. The glands contained secondary deposits.

Liver Lesions

Apart from the urinary tract the remaining tissues in this series of patients have exhibited no special susceptibility to tumour formation. In view, however, of the incidence of liver tumours, which has been noted in experimental animals, the following case is of interest:

Case VI.—J. W. L.

On January 1, 1948, this man, who had had twenty years' exposure to benzidine, was treated by perurethral diathermy for a small papilloma on the left side of the bladder. Shortly afterwards his health started to fail and he finally died on March 19, 1948. At post-mortem the liver was found to be enlarged and many carcinomatous nodules were present in it. The bladder, renal pelves and ureters appeared entirely clear of tumour. No primary carcinoma was found elsewhere in the body. It was thought that the carcinomata in the liver might be primary lesions. Unfortunately no ultimate decision could be made as no sections were prepared by the pathologist concerned.

The Mode of Action of the Carcinogens

The mode of action of the urinary carcinogens is an intriguing problem but one which could not be adequately discussed in this paper. For reviews of the work which has been carried out and extensive bibliographies the writings of Bonser *et al.* (1958), Boyland (1958), McDonald and Lund (1954), McDonald and Thorson (1956),

Scott and Boyd (1953), and Walpole and Williams (1958) may be consulted.

Prevention

In this paper the recognition of occupational bladder tumours as an industrial hazard, the methods of early diagnosis, their clinical features and response to treatment are discussed. Whilst these subjects are of great importance the ultimate objective of medicine and industry must be the complete removal of the causative factors. The ethics of the manufacture of urinary and other carcinogens has been admirably discussed by Scott (1958). Absolute prohibition of their manufacture and use would appear to be the ideal method of prevention. Such a course, however, represents an over-simplification of the problem and fails to take account of the varying severity of different hazards, of possible means of rendering manufacture safe and of the industrial importance of the product. Scott concludes: "If they are to be made, substances or processes which promote grave industrial diseases such as radiation sickness, occupational cancer or aplastic anæmia call for the maximum necessary precautions at whatever cost may be involved. If the achievement of the required standard is not practicable, complete prohibition must be insisted upon and industrial or public opinion would surely make this effective."

By 1950 beta-naphthylamine was universally recognized as a highly dangerous industrial chemical. It was also found impossible to devise plant for its production and use which afforded adequate protection and yet could be operated at an economic rate. In the United Kingdom it was voluntarily decided to abandon its manufacture. The loss would have been a serious one as beta-naphthylamine is extensively used for the manufacture of Tobias acid and similar beta-naphthylamine sulphonic acids, which are employed in the synthesis of many azo dyes. Chemists, however, found it possible, but at considerable extra cost, to alter the mode of manufacture so as to produce the Tobias acid by the sulphonation of beta-naphthol followed by amidation. The production of the carcinogen was thus avoided. Beta-naphthylamine is now no longer made in Great Britain, Germany and Switzerland. The manufacture of rubber antioxidants derived from alpha- and beta-naphthylamine has also been abandoned in this country.

Owing to the recognition of its potential dangers by Walpole *et al.* (1952 and 1954) 4-amino-diphenyl (xenylamine) has never been manufactured in this country.

Benzidine and alpha-naphthylamine are unfortunately essential intermediate compounds for the manufacture of large ranges of colours used in many industries. No substitutes or alternative methods of making the dyes have yet been devised. Manufacture therefore still continues but is carried out in specially designed plant and under strict medical supervision. Users of these compounds are also warned of their toxicity. Benzidine has also been employed in the rubber industry but its use is now discontinued.

During 1957, in order to try and ensure safe working conditions, Scott and Williams (1957*b*) drew up for the Association of British Chemical Manufacturers a "Code of Working Practice Recommended by the British Dyestuffs Industry for the Manufacture and Use of Products Causing Tumours of the Bladder". This is now accepted as the standard of practice.

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Meeting
May 28, 1960

MEETING AT THE CHRISTIE HOSPITAL AND HOLT RADIUM INSTITUTE, MANCHESTER

The following papers were read:

The Papanicolaou Technique for the Diagnosis of Vesical Tumours.—Dr. T. S. SCOTT.

Carcinoma of the Urethra: the Technique and Results of Treatment by Irradiation and Surgery.—Professor RALSTON PATERSON and Mr. D. S. POOLE-WILSON.

Grading of Bladder Tumours.—Mr. D. S. POOLE-WILSON.

Experimental Tumours.—Dr. A. L. WALPOLE.

Sarcoma of the Bladder.—Mr. M. HALL.

Multiple Papillomatosis of the Bladder.—Mr. A. ASHWORTH.

The Treatment of Multiple Papillomatosis of the Bladder by Intracavitary Irradiation and X-ray Therapy.—Dr. R. C. S. POINTON.

The following demonstrations were given:

Linear Accelerator and Betatron.

Cytodiagnosis of Bladder Tumours.

Irradiation Treatment of Carcinoma of the Glans Penis.

Localization of Bladder Tumours for X-ray Therapy.

The Use of the Image Intensifier for Control of Interstitial Irradiation of Bladder Tumours.

The following cases were shown:

Carcinoma of the Bladder Treated by X-ray Therapy.

Melanoma of the Urethra.

Carcinoma of the Urethra.

Total Removal of the Bladder and Urethra for Vesical and Urethral Tumours.

Sarcoma of the Bladder Treated by X-ray Therapy.

Diverticulum Following Interstitial Irradiation of a Tumour of the Bladder.

Total Cystectomy for Multiple Papillomatosis.

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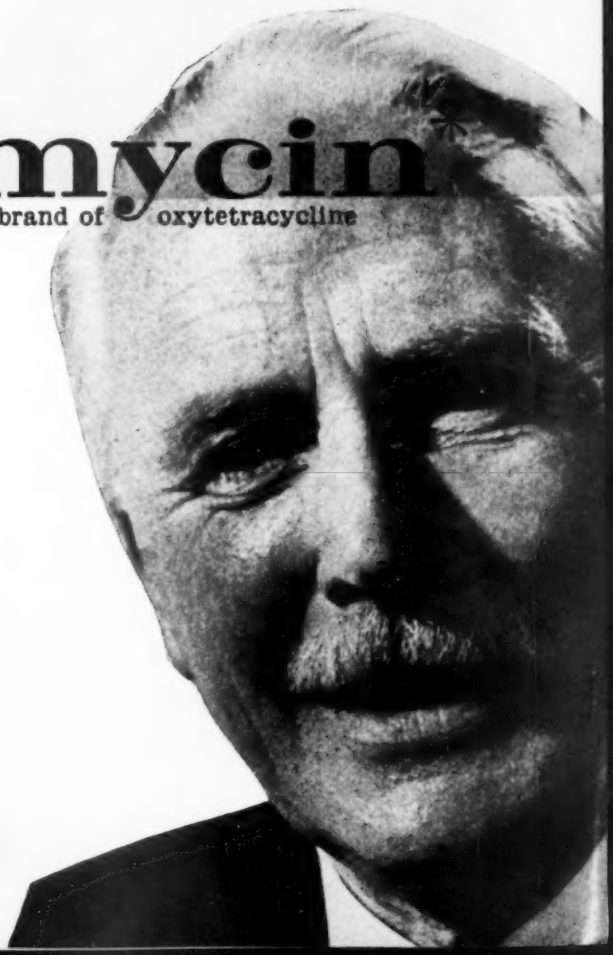
Practitioner, 1958, **181**, 684-5



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A gratifying feature of Metercal is its high satiety value. Overweight patients placed on Metercal alone comment on the absence of hunger, their improved sense of well-being and increased motivation to lose weight.[1]
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Section of Experimental Medicine and Therapeutics

President—Professor W. D. M. PATON, D.M., F.R.S.

Meeting
March 8, 1960

The Principles of Drug Action

PRESIDENT'S ADDRESS

By Professor W. D. M. PATON, D.M., F.R.S.
Oxford

THE phrase "principles of drug action" refers to those general laws, sometimes no better than general rules, deduced from experience in the use of drugs. The principles may rest on the consideration of the natural physiology of the body, may emerge from a detailed analysis of the action of particular drugs, or they may be arrived at by comparing related drugs. It may be possible to practise medicine while ignoring principles altogether. Generalities do not cover the details of daily administration; and one needs little acquaintanceship with therapeutics to know how many of the observed responses and peculiarities of patients still resist rational explanation. It is possible to be thoroughly familiar with principles of action and yet be a poor clinician. If this is true, or even partly true, why should one attach any importance to the laws and generalities to which the pharmacologist in particular strives?

The first reason is a simple practical one—that of teaching. Confronted with the huge scope of modern therapeutics, one must have some basic skeleton on which to build. One such skeleton could be simply the sort of codification to which all of us once resorted at the last moment before an examination. The aim here is not primarily to be rational but to present information in a way that the mind will, at least temporarily, remember it. However, in the end, such memoranda are unsatisfying and of only transient value. If basic knowledge is used, knowledge that will not need to be revised with the advent of further scientific advances, then a permanent investment in understanding has been achieved. The learner is prepared not only with a basis for understanding current drugs, but of understanding new ones.

But there is a possibly more important reason for getting at principles. The mind cannot work in a vacuum—if the name of a drug is mentioned to a medical man, even the most practical, there would enter into his mind not only a thought of what it does, but how it does it. Despite its somewhat academic connotations, *some* theory of drug action is, I believe, closely bonded with the substance of therapeutic practice. This idea should discipline the pharmacologist. If, by overhasty criticism, he destroys in the mind of the clinician a plausible theory of action, he must realize that, in the mental chamber now swept and garnished, seven other more devilish theories may easily enter in.

Principles can broadly be divided into two parts. The first concerns the fate of a drug in the body; that is, the manner in which it is absorbed from the point of administration, is distributed in the body, is excluded or concentrated in particular tissues, is metabolized, or is eliminated; and the time relationships of all these variables.

To a large extent, the whole of this depends on three simple properties of a drug—molecular weight, chemical stability, and the extent to which it is ionized. The first two properties have sufficiently obvious implications, but the significance of the third is not always recognized. There is now abundant evidence that, in general, the entry of a substance into a cell or its passage through a cellular barrier depends on its being able to dissolve in the fatty material of cell walls. There are many exceptions: for instance the absorption of glucose, sodium, potassium, calcium, or iron; but for these exceptions there is evidence of special transport mechanisms. In the absence of special handling, then, fat solubility will be crucial. This in turn depends (amongst other things) on ionization: if the drug is such that it readily accepts a proton (i.e. is a base) or sheds a proton (an acid), then at bodily pH a large proportion of it will be in the charged form; and in this state its water solubility rises sharply and its fat solubility declines. Suppose that a substance is strongly ionized, or even, like a quaternary salt, exists only in the ionized state. It will be poorly absorbed from the alimentary tract. Once

within the body it will live an extracellular existence, and its concentration in the blood will correspond to a distribution volume equal to the extracellular fluid. Even if it can act on the central nervous system, it will not reach it. Its failure to enter cells will limit the extent to which it can be metabolized. When it reaches the kidney, it will be filtered, but neither secreted nor reabsorbed, since both the latter involve a cellular passage. In this picture we can recognize the main features of the distribution of, say, hexamethonium or pentolinium, and streptomycin among bases; heparin and (to some extent) penicillin among acids.

On the other hand, if a significant proportion of the drug exists in the unionized state, then (like so many drugs prescribed) it is active by mouth; it distributes more or less in the body water; it may penetrate cells, there to be metabolized perhaps, or concentrated; its actions on the C.N.S. (if any) will show themselves; and it may be actively secreted or reabsorbed by the kidney. Thus one arrives at the generalization that drugs which act on the central nervous system, drugs which are cumulative, and those which interfere with the biochemical processes within the cell will be active by mouth.

One needs only to make such a statement to start thinking of the exceptions. But there is a value in keeping the general principle in mind, despite the exceptions. The very discrepancies will point to some mechanism which handles a particular drug in a special way.

The second great factor controlling distribution is that of circulation rate and tissue blood flow. One cannot survey the variables now, but there is one subtlety with intravenous injection which perhaps merits further study. When an injection is made, it does not immediately mix with the whole blood volume, but passes round as a "slug" for at least one circulation, possibly two. One might readily assume that the response by the body will be to the sustained level after these transient dilution effects are over. But Professor J. A. B. Gray and I, when studying circulation time in the cat, observed that this may not be so. The response to an injection of histamine seemed to depend wholly on the slug, and the subsequent blood level concentration to be unimportant (Fig. 1). It is a familiar observation that rapid injections have a different effect from slow ones, but if one seeks to correlate, as ultimately we should be able to do, blood levels of a drug with its action, it is probable that the "slug", with its concentration ten or more times higher than the final equilibrium concentration, will play an important role.

Another satisfactory, though approximate,

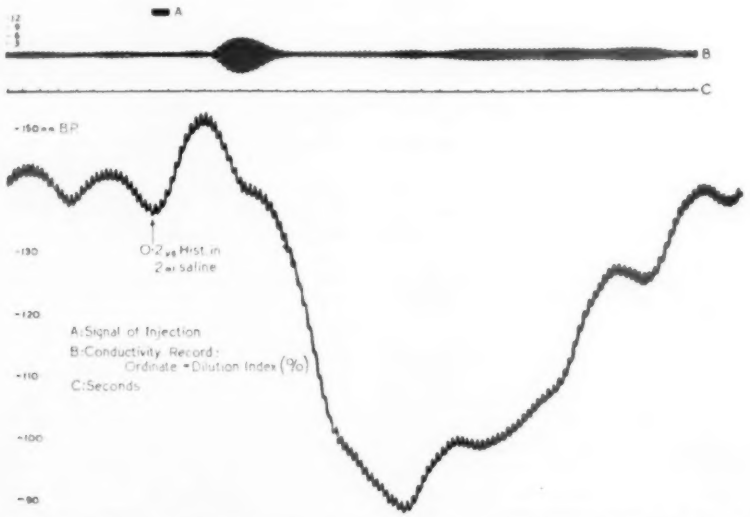


FIG. 1.—Upper tracing: record of change of conductivity of carotid arterial blood after injection of 2 ml saline containing 0·2 μg histamine, in a cat under chloralose. The change in conductivity is due to dilution of the red cells by the saline, and can be used as a measure of concentration of any substance dissolved in the saline. Lower tracing: record of arterial blood pressure. The fall in blood pressure begins about 3 sec after the appearance of the injection "slug" in the carotid, and checks 2–3 sec after the end of the "slug". The blood pressure then rises steadily, in spite of the rise in concentration of histamine in the blood as recirculation occurs (Gray and Paton, 1948).

exercise, is to deduce from first principles a justification for the habitual practice of giving drugs three times a day. If the drug lives an extracellular existence and is filtered by the kidney, then it is distributed over a space of 15 litres which is being, so to say, scavenged at a rate of 140 ml/min (the glomerular filtration rate). The situation is the same as, for instance, a submarine compartment being cleared of CO_2 by fans driving air through soda lime. We have a clearance of 1% of the space per minute, a half time of about 70 minutes, and a nearly complete clearance in 4 to 5 hours. But the drug is not usually purely extracellular, so the clearance will be a little slower, say 6 to 8 hours: 3–4 doses a day.

'But fascinating though these processes are, they form only part of the picture. Having studied how the drug gets to its site of action, how at the receptor level do drugs actually work? At once it seems helpful, where possible, to relate the action to some natural substance, whether a transmitter of action at a surface membrane, or an essential metabolite within a cell. It is curious how upon analysis so many actions eventually resolve to either the imitation of some natural substance, or more usually to its antagonist. Among the imitators are methacholine, suxamethonium, many sympathomimetic amines, and the synthetic substitutes for vitamin K. Among antagonists are competitors for the receptor groups of excitable membranes, such as atropine, phentolamine, gallamine; competitors for entry into synthetic pathways, such as the sulphonamides, or perchlorate ion or perhaps penicillin; competitors for transport, such as the hemicholiniums or probenecid or, probably, procaine (for sodium entry during the nerve impulse); competitors *for* binding sites, as histamine liberators and perhaps reserpine; or competitors *with* binding sites, as BAL, protamine; competitors for destructive enzymes, as eserine, iproniazid, aminoguanidine.

The heart of the problem of drug action seems then to be here, in the laws according to which a chemical substance combines, or does not combine, with some receptor group (whether this leads to excitation, transport, synthesis, destruction, displacement of some other substance or binding). At this level the problems of how antibiotics act and how atropine works become the same, with the great question—what is the nature of the receptor for which each substance competes?

Here is one of the humiliating paradoxes of pharmacology: we believe in "receptor groups": and yet they are still purely hypothetical entities, unseen by eye or microscope, evidenced only by circumstance. We can as yet only study the way they behave, and try to construct plausible models accordingly. What models have we, first for stimulant action, and second for interference with excitation by an antagonist? I will discuss this generally, omitting any account of our knowledge of what specific chemical configurations confer particular actions, or of the extraordinary specificity whereby one can, with a suitable drug, dissect out the finest details of the structure of a membrane.

The first successful proposal for a general theory of drug action was made by A. J. Clark: that the stimulants occupied specific receptors, and that the response depended on the proportion occupied. One could then apply a relation developed by Langmuir for the adsorption of gases on metals, the Langmuir isotherm, which also applies to many enzyme concentration-velocity curves. Subsequently J. H. Gaddum pointed out that this approach could be extended to antagonists, if one supposed that the antagonist filled receptors without activation. But there was a problem. On the one hand, Gaddum found that in the presence of an antagonist (here ergotoxine against adrenaline on a piece of rabbit uterus), you could still run the gamut from a threshold to a full maximal response, just as you could on the normal tissue, with the same ratio of threshold to maximal dose but with all the doses scaled up by a constant factor. In pharmacological jargon, the log-dose response curves were parallel. This is satisfactory if there is simple competition between the molecules, and if the stimulant can displace the antagonist from the receptors. But when an attempt was made to *demonstrate* such a displacement it could not be shown; for instance, in a frog's heart recovery from atropine cannot be hastened by applying acetylcholine to it (although its effect can be temporarily overcome). Also, why, if the antagonist is displaceable simply by increasing the amount of stimulant, does it take so long to disappear from the tissue when it is removed from the bathing fluid?

One might, on the other hand, accept the evidence that the antagonist was relatively firmly bound. In that case, how is it possible that a normal maximal response is obtainable with 90%, or even 99%, of the receptors occluded? The dilemma in short, is this: that there was direct evidence that the antagonists did not get displaced, yet a maximal response could be obtained as though they were.

This dilemma can be met by a new postulate; that it is not necessary for all the receptors to be occupied for a full response to occur—the postulate, in short, of "spare" receptors. If as many as 99% are spare, then not until a 100:1 antagonism has been exceeded will it be impossible

to produce the full maximal response. This resolves the problem, although it leaves one with a disconcerting surplus of receptors.

But there are other problems. Why is one drug a stimulant, another an antagonist? If the latter can attach to a receptor group, why does it not excite? Is the receptor capable of two different kinds of union, even though the stimulant and the antagonist may be of great chemical similarity? Further, why are some stimulants less effective than others, producing a smaller maximal effect than others? The suggestions here, from E. J. Ariens in Holland and from R. P. Stephenson in Edinburgh, have been that drugs have varying "intrinsic activity" or "efficacy"; that receptor unions with them lead to more or less excitation for the same number of unions. The good stimulant has high efficacy; the less effective stimulant, a medium efficacy (and in so far as it occupies receptors without exciting fully it is an antagonist to some more active stimulant); the antagonist, zero efficacy. We have to envisage a whole series of drug-receptor unions with varying properties, somehow accommodated within what must be very similar chemical reactions.

The picture, now, is still of Clark and Gaddum's receptor occupation, with the qualifying assumptions of a surplus of receptors, and of receptor occupations of varying effectiveness. Can we now describe drug action satisfactorily? I think not. Let us examine some other features of drug action. Why, with nicotine, is there *first* excitation then block? Why is there a general association among blocking agents of high potency with slow onset of action and slow offset? Why does it seem impossible with any stimulant to produce a fully sustained excitation? How does varying "efficacy" come about among similar molecules?

It is questions such as these, especially the peculiarities of nicotine, which have prompted me to explore a theory of drug action based on one different premise. The assumption so far has been that, with a stimulant drug, it is the *occupation* of a receptor which brings about excitation. Let us make a different assumption: that it is the act of combination with a receptor that excites, but only momentarily. Once combined, no further excitation occurs; but in so far as a receptor is now occluded, the occupying drug molecule is blocking further combinations. Instead of thinking of the receptor as, say, a note on an organ, such that as long as it is depressed a note is emitted, we think of it like a piano, one burst of sound and then silence.

What are the differences between the theories? On what I shall call "rate" theory (as opposed to "occupation" theory) the kinetic constants of the system become crucial, in particular the constant which characterizes the rate of release of drug from the receptor, the dissociation rate constant. Suppose we have two drugs, both combining with similar rate constants, but one dissociating a thousand times more slowly; and suppose we choose concentrations of each to give equal, say 50%, receptor occupation; because of the tenacious binding and slow dissociation of the second one, it will achieve this occupation at a much greater dilution than the first. Thus although the two molecules achieve equal *occupations*, the slowly dissociating one achieves a far lower *rate* of combination. Indeed, the maximum equilibrium activity possible is directly proportional to the dissociation rate constant. We reach a first prediction, that any drug which dissociates slowly will be a correspondingly feeble stimulant; and strong stimulants should "wash out" quickly, antagonists slowly.

A second point: on rate theory, a stimulant action should be maximal at first exposure to a drug, when the receptors are all free. Then as they become occupied the rate of combination must fall off, until an equilibrium is reached, dictated primarily by the rate at which dissociation frees receptors. With *all* stimulants, therefore, there should be what for brevity one may call "fade"; and this "fade" should have a time course corresponding to that of the rising occupancy (to which in fact it is due). Another implication follows. Suppose the drug is washed out, after fade has developed. There is now none in the bath fluid, but some receptors are still occupied. On occupation theory, there should be a residual *excitation*, passing off with time; on rate theory, activity should cease at once, and a residual *antagonism* be left.

Finally, we must bring out explicitly a point already implied. On rate theory, the time course of a drug's action should be linked directly not only to the *nature* of its action but also to its potency. One should, for instance, be able to estimate the potency of an antagonist from the speed with which its action comes on and wears off. Further, the shape of these curves should be of the same form; to be explicit, and omitting the mathematics, the rate of recovery should always have time constant K_2, and the rate of onset should always be K_2 multiplied by the dose-ratio finally achieved. Thus with a series of similar drugs of varying activity, if we produce equal blocking actions with them, the actions should have the same shape, with suitable expansion and contraction of time scale.

So much for theoretical background. How can we put such ideas to the test of quantitative experiment? We must have a preparation giving

a rapid graded measurable response to suitable stimulants, under conditions where concentrations applied are exactly known, and controlled. It means, in this context, a strip of guinea-pig ileum in an isolated organ bath writing on a smoked drum.

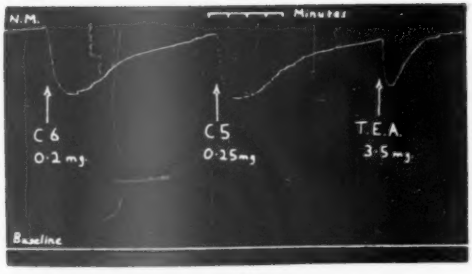
I shall not describe the experiments further, but simply state that one can verify the theoretical predictions. Thus in a series of related drugs, stimulant activity varies directly and antagonist potency inversely with ease of dissociation from tissue binding; among stimulants one finds that activity is highest at the beginning of the exposure, and dwindles thereafter; in general the kinetics of action link quantitatively with the potency and the character of the action seen.

Some of these results have clinically familiar parallels. Thus it is at first sight a surprising thing that in general the more potent drugs do not act faster, but slower, than less potent ones. With the cardiac glycosides, for equal maximal effects, those with slowest onset of action (such as digitoxin) also take the longest time to reach their peak and to wear off; the quickest (e.g. strophanthin) in onset is also quickest in peak and offset. So too with the dicoumarol group, one can construct a series such as dicoumarol (slow), phenindione (medium), ethylbiscoumacetate (fast). With ganglion-blocking agents the shape of the response, despite variations of time course of considerable size, remains the same (Fig. 2).

Another parallel is this: with many blocking agents there are often vestiges of stimulant action to begin with. Is this part and parcel of their action, or, so to speak, a contaminant? On rate theory it is part of their action, for the initial combination of the antagonist with receptors should lead to *some* measure of excitation, the question being simply whether it is detectable or not. With drugs like ergotamine, and indeed nicotine, it is substantial and we have a mixed drug. But with others, like phentolamine, *d*-tubocurarine, or even hexamethonium, under certain experimental conditions this vestigial excitation is detectable. I like to think it is detectable even with a drug like penicillin: for if a bacterial culture is repeatedly subcultured on deficient media and at temperatures lower than normal, in other words when the organisms are old, cold, and hungry, penicillin will then stimulate their growth.

I have said little, so far, about the familiar powerful stimulants such as acetylcholine or histamine. They are difficult to study in terms of rate theory for *ex hypothesi* they must dissociate very rapidly, and their kinetics will be too fast to follow. In general their behaviour conforms with this, with one important qualification. If a *large* dose of acetylcholine (or histamine) is applied to a piece of smooth muscle, and then washed out, the tissue is afterwards relatively insensitive. Are these stimulants, then, also blocking agents, like atropine or

A



B

FIG. 2.—Comparison of the time courses of action of ganglion-blocking agents on the response of preganglionically excited nictitating membrane in the cat under chloralose. Intravenous injections. Time in minutes. A, at first arrow, 0·19 mg hexamethonium: at second arrow 0·17 mg pempidine (reproduced from Corne and Edge, 1958, by kind permission). B, injections of 0·2 mg hexamethonium, 0·25 mg pentamethonium, and 3·5 mg tetraethylammonium respectively (reproduced from Paton and Zaimis, 1949, by kind permission).

mepyramine? We can reject this, at least on smooth muscle and I suspect on other tissues, for a simple reason; the insensitivity is not a *specific* receptor insensitivity. It extends to any other stimulant, and it is a function, not of the dose of stimulant given, but of the response obtained. If it is not a receptor function, then it represents some incapacity by the tissue to maintain its responsiveness in the face of continued chemoceptive activation. Indeed, desensitization is detectable after quite brief exposures to moderate doses of stimulants, and it must be presumed to be present *during* such, or greater, responses. The idea of "spare" receptors was mentioned earlier to explain how maximal responses could still be obtained when many receptors were occluded. The existence of desensitization is relevant here; for although the postulate of spare receptors does not predict the existence of desensitization, the existence of desensitization requires that there should be spare receptors. For if desensitization is present in any substantial response, it will be especially marked during the so-called maximal response, and this will be limited, not by receptor behaviour, but by the tissue's capacity to respond to a very high degree. The maximal response will thus be recorded before all the receptors are maximally excited. If we occlude many of them, the maximal response will still be obtained if there are sufficient, each now excited at a higher rate, to produce the same total activity. The idea of spare receptors (or, on rate theory, spare receptor capacity) thus remains valid, but perhaps with the wrong connotation. For it suggests simply a surplus, a large safety factor, ensuring that the tissue will be exposed, when necessary, to full chemoceptive action. But it appears that the implication of desensitization is different; that prolonged chemoceptive action is a state harmful to the tissue, and that the mechanism of desensitization protects the tissue from the ravages of excessive chemical stimulation. Usually chemical excitation is a transient affair of milliseconds, not seconds or minutes. If we could test it, the proportion of apparent spare receptors would probably be small if very brief responses were studied, and increase steadily as exposures were prolonged.

One last point: the rate theory of action seems likely to be especially involved with potassium movements. This led to a comparison between the effects of desensitization and potassium deprivation. They seem remarkably alike. Both lead to non-specific loss of responsiveness. Lack of potassium deprives a tissue of its ability to recover from desensitization. Vigorous chemical stimulation accelerates the effects of potassium lack. Recovery from both takes the same time course. It is tempting, knowing that smooth muscle loses potassium under the action of these stimulants, to postulate that desensitization is due to loss of intracellular potassium.

With desensitization thus studied, there are again clinical counterparts—the results of overtreatment of the myasthenic patient with neostigmine, the progressive failure of the intestine in ileus to respond to stimulants, the phenomenon of adrenaline shock. In all these one would anticipate a contribution, at least, by this waning sensitivity to stimulants, consequent on prolonged exposure.

The view of drug action, then, which seems best to meet many of the observations, is simply that stimulant action of a drug depends on rate of combination; that therefore, after initial exposure, activation depends on rate of receptor freeing by dissociation; that if the dissociation rate is hindered, for instance by the non-specific binding forces present with large or fatty molecules, antagonism prevails; that in addition smooth muscle at least becomes, non-specifically, insensitive, if chemical excitation is large or persistent. Stimulant action depends on a dynamic make-and-break between drug and receptor; antagonism on its hindrance. Given this, we can link speed of action, potency, character of action, speed of offset, simply with the aid of two determinable rate constants. If this is true, it is these rate constants which we must correlate with chemical structure; which we must adjust, to obtain drugs of the right duration and type of action; and which give us our closest information about the still mysterious receptors.

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Section of Medicine

President—E. R. CULLINAN, M.D.

Meeting
April 26, 1960

DISCUSSION ON THE ACQUIRED MYOPATHIES

Sir Russell Brain (London):

Clinical Aspects

As yet there is no satisfactory classification of diseases of muscle. There are several reasons for this. We are still often ignorant, or partly ignorant, of their ætiology. At present no satisfactory classification can be based on the pathological appearances, because it is not certain that what appear to be pathological differences may not sometimes be related to different stages of the same disease rather than to different diseases. Conversely, it is possible that similar pathological changes occur in different disorders. Nor can electromyography as yet help us much, for though in clear-cut cases it may be a valuable aid in distinguishing a neurogenic from a myopathic muscular wasting, we are hardly yet in a position to distinguish by means of electromyography one form of myopathy from another. In the present state of our knowledge, therefore, in making what can only be a provisional classification of muscular disorders we have to take into account all that we can learn about heredity, clinical features, endocrine and biochemical abnormalities, muscle pathology, usually ascertained by biopsy, and electromyography. And any such provisional classification will in my view have left over a probably heterogeneous group of cases which do not fit into any established category.

I shall start with a list of the main varieties and say something about those in particular which constitute important clinical problems or throw light upon the nature of these myopathies as a whole.

TABLE I.—THE MYOPATHIES OF LATE ONSET

(1) Miscellaneous infections: Bornholm disease, trichiniasis, &c.
(2) Polymyositis (dermatomyositis, neuromyositis)
(3) Associated with collagen and allied diseases: polyarteritis nodosa, disseminated lupus, rheumatoid arthritis
(4) Sarcoidosis
(5) Associated with thyroid disease: acute thyrotoxic myopathy, chronic or relapsing thyrotoxic myopathy, thyrotoxic periodic paralysis, myxœdema
(6) Exophthalmic ophthalmoplegia
(7) Myasthenia gravis
(8) Associated with miscellaneous endocrine and metabolic disorders: acromegaly, Addison's disease, Cushing's disease, aldosteronism, hypokalæmia, hyperkalæmia, steroid therapy
(9) Associated with carcinoma
(10) Heredofamilial dystrophy
(11) Myohæmoglobinuric myopathy
(12) Cryptogenic, including ocular myopathy

I take the acquired myopathies to mean those disorders of muscle which are not secondary to disease of the nervous system, and which are not the result of an inherited predisposition. Both classification and diagnosis are made difficult by the fact that some of the hereditary muscular dystrophies may arise in adult life. I have therefore prepared a table of the myopathies of late onset (Table I).

Polymyositis has become established as the name of a diffuse disorder of muscle which may or may not be clinically associated with dermatitis. Even when the skin appears clinically normal, it may be histologically abnormal. This is often a subacute disease beginning in the proximal limb muscles. It may run a relapsing course or settle down into a chronic one, which raises the question whether a myopathy which runs an insidiously progressive course from the beginning is nosologically identical with polymyositis. It is not surprising that nerve endings in muscle should be involved in polymyositis. There is, however, rarely a simultaneous involvement of some peripheral nerves in polymyositis, leading to sensory symptoms and signs of peripheral nerve distribution. The term neuromyositis should be limited to this association.

Myopathy is only an incidental result of *polyarteritis nodosa* and *disseminated lupus*. It may be responsible for muscular weakness and wasting in rheumatoid arthritis, and if, as occasionally happens, the muscular symptoms predominate at first, the diagnosis may be difficult until the joint lesions appear.

Sarcoidosis of muscle raises an interesting question. It has long been known that in a patient suffering from sarcoidosis the characteristic pathological changes may involve muscles, but there are also cases in which the characteristic histological changes of sarcoidosis have been found in muscles of patients who have shown no other evidence of sarcoidosis—for example in carcinomatous myopathy and in chronic progressive myopathy associated at the onset with thyrotoxicosis. Is this sarcoidosis limited to the muscles, or are the histological changes in the muscles a pattern reaction which may be due to many causes?

Thyrotoxic myopathy may develop acutely, but more often insidiously *pari passu* with the thyrotoxicosis. There is usually a rapid response to treatment of the thyrotoxicosis but not always. In severe acute cases neostigmine may give valuable symptomatic relief. Thyrotoxic periodic paralysis characterized by brief attacks of severe muscular weakness is rare. Myopathy may be a symptom of myxœdema, and indeed it may be the symptom which brings the patient under observation. In myxœdema the muscles tend to be enlarged and firm, though weak, and they exhibit myotonia on mechanical and electrical stimulation. The response to the treatment of the myxœdema is usually good.

Exophthalmic ophthalmoplegia is still of uncertain ætiology, but, though the patient may be thyrotoxic, in true exophthalmic ophthalmoplegia the muscular weakness is due to changes which are independent of the thyrotoxicosis. The presence of thyrotoxicosis, however, may give rise to a difficulty in diagnosis because occasionally thyrotoxic myopathy may affect the ocular muscles.

Myasthenia should now be regarded as a symptom, and myasthenia gravis as a disease characterized by myasthenia as its cardinal symptom. In its typical form *myasthenia gravis* is usually easily recognized, since it is distinguished by muscular fatigability of characteristic distribution temporarily relieved by neostigmine and similar drugs. But muscular wasting, though not commonly present in typical cases, may occur in myasthenia gravis, and when associated with diminution or loss of tendon reflexes may lead to confusion with one of the other myopathies. Moreover, when myasthenia gravis co-exists with thyrotoxicosis, there may be some doubt as to which disorder is responsible for the muscular weakness. A similar difficulty arises in those rare cases in which myasthenia gravis is associated with exophthalmic ophthalmoplegia.

Muscular weakness and wasting are occasionally severe and incapacitating in *acromegaly*, and may be the presenting symptom in *Addison's disease*. Muscular weakness may occur also in Cushing's disease, and in aldosteronism. Either a very low or a very high blood potassium may interfere severely with muscular function, and each produces characteristic changes in the electrocardiogram. I have seen cases in which the hyperkalæmia is itself an indirect result of a myopathy, the myopathy causing respiratory failure with CO_2 retention, and this in turn leading to a sharp rise of blood potassium which intensifies the muscular weakness. The occurrence of muscular weakness as a result of steroid therapy is worth noting. It has been reported with both triamcinolone and with fludrocortisone.

It is now recognized that rarely carcinoma may in the absence of metastases produce unexplained disturbances of function of the nervous system at any level and of the muscles. Excluding muscular wasting secondary to lesions of the lower motor neuron there remains a small group of patients suffering from *carcinomatous myopathy*. Weakness and wasting tend to affect the proximal muscles first, but the ocular and bulbar muscles may also be involved. There may be a myasthenic element in the clinical picture responding to neostigmine, and the weakness is occasionally precipitated or exacerbated by a muscle relaxant. Although in such cases the muscle disorder may be part of a dermatomyositis, this in our experience is rare and in most cases the histological picture either at biopsy or post-mortem is non-specific. One patient who had both carcinoma and a tuberculous infection of the lung showed in the muscle the histological picture of sarcoidosis.

There is ample evidence that progressive myopathy in middle age or later may be *heredofamilial* in origin. I have records of four families of this kind, the age of onset in my patients being in 2 cases at 35, in 1 at 38 and in another at 43. In such cases the myopathy is usually of the limb girdle type, affecting first the proximal muscles of the limbs and spreading to the distal muscles and trunk. The Duchenne type of muscular dystrophy is not encountered after childhood, but pseudo-hypertrophy of muscles is not peculiar to that type and may be encountered in any variety and at any age. The recognition that heredofamilial myopathy may develop in middle life naturally raises the question whether cases of myopathy of late onset without a family history may sometimes be sporadic manifestations of a hereditary disorder. Obviously the later in life such a disorder develops the more difficult it must be to establish a familial incidence because other members of the family who might have developed the disorder may have died before they have reached the appropriate age.

I have included *myohæmoglobinuric myopathy* because, though rare, it is of considerable interest. The affected muscles are painful, weak and swollen and myohæmoglobin appears in the urine. The cause is unknown and attacks may sometimes be precipitated by exertion. There appears to be a hereditary tendency in some cases.

There remains what is almost certainly a mixed group of patients with muscular disorders which do not fit into any of the previous categories. I have records of over a dozen of these, both sexes being equally affected and the age of onset ranging from 40 to 74. It includes patients in whom the ocular muscles are affected alone (ocular myopathy) or with other muscles. The

bulbar muscles may be involved with or without the muscles of the limbs and the trunk, or the latter may alone be affected. The course of the disease is progressive but may extend from five to fifteen years. The electromyogram is characteristic of a myopathy and the histological changes are usually described as being those of a myopathy rather than polymyositis. Some no doubt would classify these patients as suffering from hereditary muscular dystrophy of late onset. Others would describe the condition as a chronic form of polymyositis. I suspect that they will prove to be of mixed ætiology. For the present they are perhaps best labelled *cryptogenic*.

Dr. A. T. Richardson (London):

Electromyographic Studies

The electromyographic diagnosis of lesions of voluntary muscle fibres—the myopathies—is based on the detection of dysfunction of these fibres, as evidenced by abnormalities of their electrical activity on volition. On this basis, such acquired lesions as myasthenia gravis and some forms of periodic paralysis, where signs of muscle fibre degeneration are usually absent, have features in common with polymyositis and the myopathies associated with carcinoma, thyrotoxicosis and adrenocorticosteroid therapy where, in contrast, evidence of muscle fibre degeneration can usually be found. In this paper, therefore, the electromyographic characteristics of muscle fibre lesions in general will first be described, and then particular reference made to myasthenia gravis and polymyositis, which are examples of myopathies in which the electromyogram is not only of value in diagnosis, but also contributes to an understanding of their pathogenesis.

The Electromyographic Diagnosis of Myopathies

In clinical practice, electromyography consists of the sampling of a muscle by the use of an intramuscular needle electrode to detect various action potentials which are identified with a cathode ray oscilloscope, loud speaker or frequency analyser. Fig. 1 illustrates the anatomical basis of those muscle action potentials relevant to the diagnosis of the myopathies. Fig. 1A shows the action potential derived from a single muscle fibre—the fibrillation potential. It is usually a diphasic spike of 1 to 1·5 milliseconds (msec)

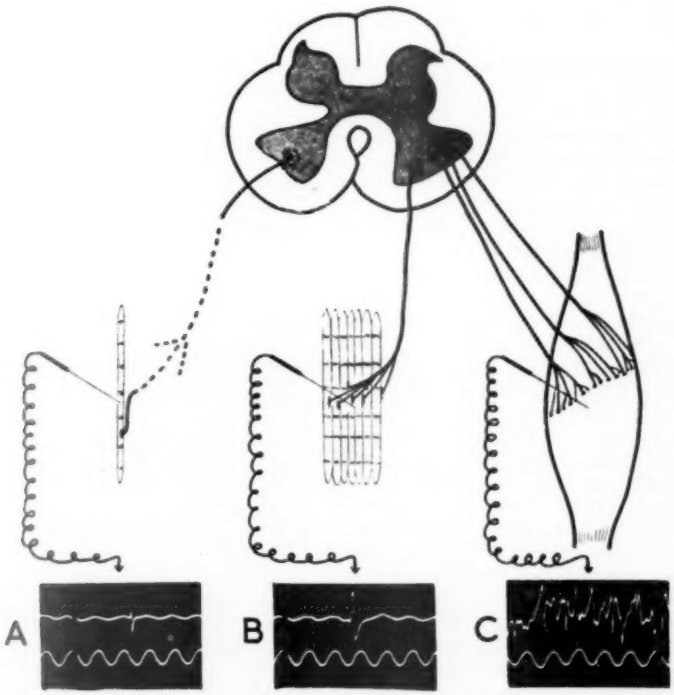

FIG. 1.—Diagram to illustrate the anatomical basis of muscle action potentials. A, fibrillation potential, B, normal motor unit potential, C, normal interference pattern. Calibrations 50 cycles at 300 microvolts.

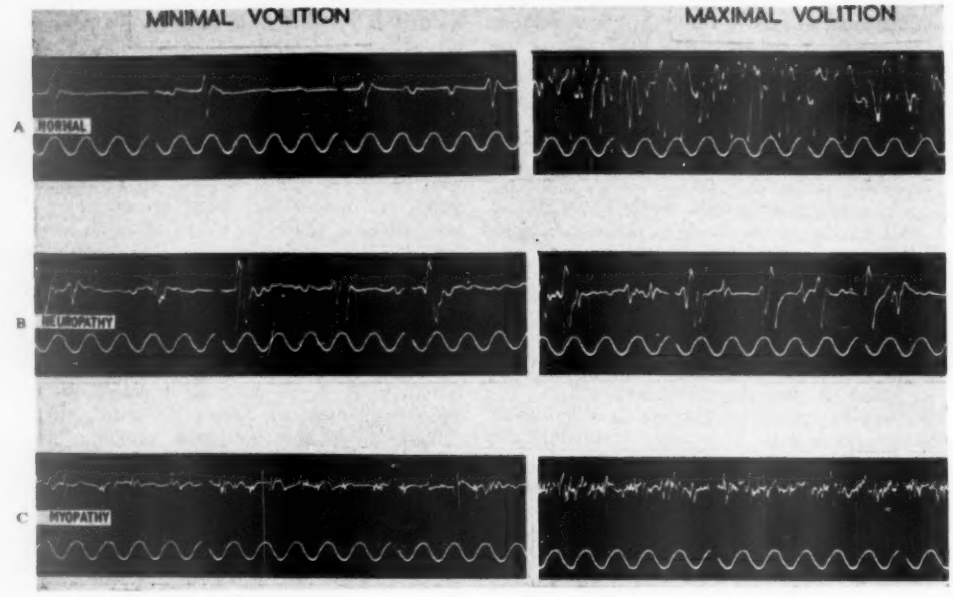

FIG. 2.—Electromyographic patterns on minimal and maximal volition. A, normal muscle. B, a neuropathy. C, a myopathy. Calibrations 50 cycles at 300 microvolts.

duration and 20 to 300 microvolts (μV) amplitude. While not found in normal muscle, which is electrically silent at rest, repetitive fibrillation activity occurs spontaneously at a frequency of 2 to 30 per second in recently denervated muscle. Fig. 1B illustrates the action potential derived from an average motor unit, the group of muscle fibres supplied by a single lower motor neuron. Such a potential arises on volition from the almost synchronous contractions of all those muscle fibres and usually consists of a di- or triphasic wave form of 5 to 10 msec duration and 500 μV to 1 millivolt (mV) amplitude. Even in the large proximal muscles, however, there is a complement of short duration (1–3 msec) forms and up to 10% may be polyphasic. In some muscles such as the external eye muscles, these forms predominate. Fig. 1C illustrates the electrical activity of a normal muscle on full volition. This derives from the asynchronous subtetanic (20–30/sec) activity of the several motor units within the range of an exploring intramuscular electrode and consists of the summation of their potentials into the so-called interference pattern.

The electromyographic criteria of *normal muscle* are electrical silence at rest, the appearance of normal motor unit potentials on minimal volition and their summation into an interference pattern on maximum volition (Fig. 2A). In a *neuropathy* there is inactivity of the lower motor neurons and consequent loss of activity of all the muscle fibres supplied by the affected neurons. The electromyographic characteristic is therefore a reduction of the total number of motor unit potentials as shown by a failure to achieve a full interference pattern on maximal volition. Any residual motor unit potentials are of normal or greater than normal dimensions (Fig. 2B). In addition, lesions of lower motor neurons may be indicated by the appearance of a variety of forms of spontaneous muscle electrical activity, derived either from irritation or degeneration of those neurons, and by changes in nerve conduction and in the excitability characteristics of the muscle. In a *myopathy* it is the dysfunction of the individual muscle fibres within the motor unit which produces the characteristic electromyogram. There is, except in a severe lesion, retention of the total number of motor unit potentials and consequently of the interference pattern obtained on full volition. The individual motor unit potentials, however, are smaller than normal, their durations being reduced to 1–3 msec and their amplitudes to below 500 μV (Kugelberg, 1949) (Fig. 2C). An increase in the number of polyphasic forms also occurs. These features are common to all myopathies, familial and acquired. Fig. 3 illustrates the typical electromyograms from cases of myasthenic myopathy (A), thyrotoxic

myopathy (B), and the myopathies associated with triamcinolone therapy (C), and carcinoma (D).

Two technical considerations relevant to the interpretation of electromyograms in myopathies are noteworthy. The first, illustrated in Fig. 3D, is the occurrence of long duration polyphasic motor unit potentials interspersed amongst the typical short duration myopathic potentials. This temporal dispersion of the muscle fibre potentials of the motor unit appears to arise from collateral innervation or from a disturbance of terminal neuron or muscle fibre conduction. The practical importance is that it may occasionally dominate the electromyogram and imitate a neuropathy wherein disturbances of terminal neuron structure and conduction, particularly during regeneration of the neuron, produce a similar picture. This error in diagnosis can usually be overcome by a more thorough sampling of the muscle and the detection of areas where the myopathic change is uncomplicated. Another consideration concerns the detection of lesions affecting minimal numbers of muscle fibres. This is difficult because the detection of small changes in the duration of motor unit potentials, which normally show a wide scatter, requires large samples. Such a sampling would involve a prolonged and most uncomfortable technique unacceptable for clinical work. One

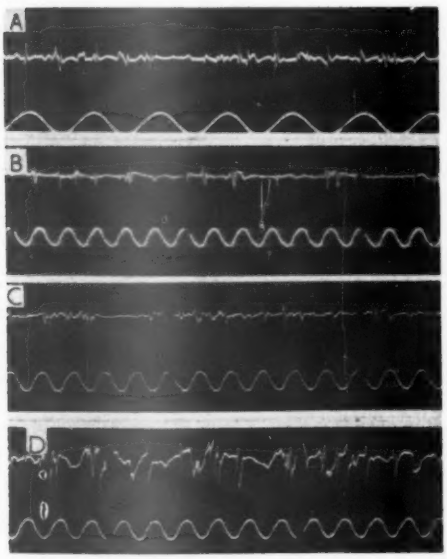

FIG. 3.—Electromyograph from: A, myasthenic myopathy, B, thyrotoxic myopathy. C, myopathy associated with triamcinolone. D, carcinomatous myopathy. Calibrations 50 cycles at 300 microvolts.

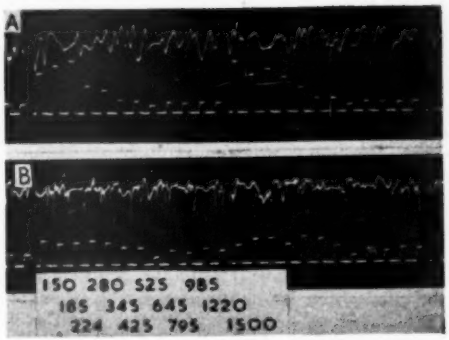

FIG. 4.—Frequency analysis of electromyograms from: A, normal muscle. B, myopathy. Frequency components in kilocycles illustrated.

method, yet to be fully developed, which may offer a solution to this problem invokes the use of a frequency analyser. This apparatus scans a selection of motor unit potentials and analyses their frequency components in the range 0·150 to 1·5 kilocycles (kc). It is found that the frequency components at and above 0·425 kc are significantly increased in the presence of small and polyphasic motor unit potentials, an increase which is the hall-mark of a myopathy (Fig. 4).

Myasthenia Gravis

While in this disorder of muscle a myopathic pattern is constantly obtained in wasted muscles, it is an inconstant finding in cases showing variable fatigability without persistent weakness or wasting. For instance, Pinelli and Buchthal (1953) found a myopathic pattern in myasthenic muscles in only 2 of their 6 cases and while Simpson (1956) detected it in the absence of wasting he supports Lundervold's (1954) and Denny-Brown's (1953) view that the usual appearance is of a derecruitment of whole motor units on fatigue. The restoration by neostigmine or Tensilon of an interference pattern of normal unit potentials from the myopathic pattern of myasthenic muscles is similarly not constant enough to be of diagnostic value, but when obtained it supplies convincing evidence that the short duration and polyphasic potentials characteristic of a myopathy are in fact derived from a failure of individual muscle fibres to contribute to the whole motor unit potential.

Because of the inconstant finding of a myopathic electromyogram in myasthenia, there has been a search for further techniques. In general, these derive from Jolly's (1895) description of the failure in myasthenia gravis of the muscle response to a repetitive faradic (indirect) stimulation but not to galvanic (direct) stimulation,

They are based on a study of the integrated muscle action potential produced by supramaximal nerve stimulation, with particular reference to variations in the amplitude of the potential during and after repetitive stimulation (Lindsley, 1935), and in its response to neostigmine, Tensilon or curare (Jarrett *et al.*, 1948).

A recent addition to these tests is the measurement of the response of myasthenic muscles to decamethonium iodide (C 10) (Churchill-Davidson and Richardson, 1953). The diagnosis of myasthenia by this technique depends upon the production by decamethonium of a neuromuscular block with some of the features of competitive inhibition (curare-like block) in the clinically weak muscles of myasthenics, and the demonstration of a remarkable tolerance to this drug in the clinically normal muscles. In contrast, the response of the muscles of normal people to decamethonium consists of the production of a pure depolarization block. Although these reactions can be demonstrated clinically during volitional activity, they are best shown electromyographically. The technique then consists of the measurement (peak to peak) of action potentials produced by the hypothenar muscles in response to supramaximal stimulation of the ulnar nerve at 10/sec before and after 2·5 mg of decamethonium given intravenously in divided doses over eight minutes. It is found that the action potential of normal muscle is invariably diminished or abolished with this dose and, in confirmation of the existence of depolarization block, is further diminished or abolished by a subsequent 10 mg intravenous dose of Tensilon. In complete contrast, myasthenic muscle retains its potential or, in the event of a reduction, shows Tensilon reversibility indicative of a competitive inhibition type of block.

Some aspects of this characteristic response of myasthenia muscle to decamethonium demand further consideration. As a diagnostic test it has the advantages of having a clear cut end-point and of being independent of the presence at the time of examination of any weakness or excessive muscle fatigue. Most important of all it seems to be a constant finding and persists in remissions of the myasthenia, either when they occur naturally or in association with thymectomy. Somewhat surprisingly, it is also remarkably specific for myasthenia gravis. Thus, it is not found in a wide variety of other neuromuscular disorders including polymyositis, even when this shows myasthenic-like features.

As regards the nature of the abnormality in myasthenia, it was the study of the action of decamethonium which first led to the suggestion (Churchill-Davidson and Richardson, 1953) that an abnormal end-plate response to acetylcholine, whose depolarization action is analogous to that of decamethonium, was responsible. The work of Grob *et al.* (1955) in which they compared the action of acetylcholine in normal and myasthenic subjects supports this theory. They found in both groups that following transient stimulation of motor unit activity and depression attributable to the depolarizing action of acetylcholine, there ensued a secondary depression attributable to the choline released as a result of the hydrolysis of acetylcholine. The important feature was that while this secondary depression had the properties of a depolarizing block in normal subjects, it had those of a competitive block in myasthenia. Further evidence indicating the essential nature of the defect of neuromuscular transmission in myasthenia derives from morphological studies of the motor end-plates in this disorder. Cœrs and Desmedt (1958) reported that in patients with generalized myasthenia methylene-blue intra-vital staining indicated a specific anomaly of the terminal arborizations of the motor nerve. Cœrs and Woolf (1959) have similarly recorded further cases showing this change and MacDermot (1960) has not only confirmed the presence of abnormal end-plates in myasthenia but has demonstrated them in muscles abnormal only in their response to decamethonium.

It seems, therefore, that there is in myasthenia gravis a structural change in the distal nerve fibres and in the motor end-plates associated with a capacity to respond abnormally to decamethonium and that this exists throughout all the muscles. It follows from this and from further experimental work that the defect of the motor end-plates in myasthenia can lead to the production of a competitive inhibition neuromuscular block by choline released by the hydrolysis of acetycholine—a state of affairs that explains all the clinical and electromyographic features of the disorder. Yet to be explained is the persistence of the abnormal response to decamethonium in remissions and its presence with morphologically abnormal end-plates in the clinically normal muscles of myasthenia. It may be that there is a varying degree of change in the end-plates with clinical evidence of weakness confined to those severely involved. Alternatively, it may be that there is more than one factor in the pathogenesis of myasthenia gravis so that the characteristic muscle fatigue is produced by a variety of insults, including perhaps thyrotoxicosis and carcinoma, but determined by a constitutional abnormality of the motor end-plates.

Polymyositis

While all the evidence is against the existence of any electromyographic change in association

with interstitial nodular polymyositis, the supervention of parenchymatous muscle fibre damage leads to the development of the characteristic disintegrated (myopathic) motor unit potentials. A particular feature is the finding of additional electromyographic features in approximately half of such patients. These take the form of spontaneous muscle activity which may be accompanied by changes in the excitability characteristics of the type usually associated with lower motor neuron degeneration. Also there is often a predominance of large polyphasic motor unit potentials in the interference pattern, a phenomenon again probably derived from changes in the neuron. The spontaneous activity assumes three forms (Fig. 5): fibrillation potentials which

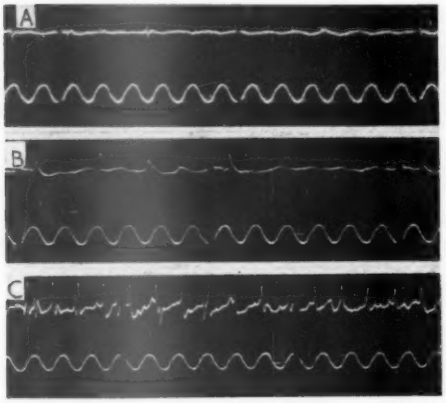

FIG. 5.—A, fibrillation potentials. B, positive potentials. C, high frequency discharge. Calibrations 50 cycles at 300 microvolts.

already have been described, positive potentials and so-called high frequency discharges. Positive saw-tooth potentials consist of a short initial positive deflection followed by prolonged negative phase of some 20–50 msec duration. Their voltage shows remarkable variation as does their frequency. Their relation to fibrillation potentials appears to be that of a decayed form of fibrillation potential. High frequency discharges consist of protracted trains of oscillations of a variety of forms which are most easily identified by their change of pitch, their initial frequency often reaching 150/sec and dropping down to 10–20/sec. While they occur in profusion in the myotonias they may be also found in a number of other conditions, particularly in polymyositis but rarely in the muscular dystrophies.

The association of short duration motor unit potentials characteristic of a myopathy, combined with the classical signs of lower motor neuron degeneration was first delineated by Bauwens in 1949 and designated by him distal neuronitis. Guy *et al.* (1950) and Lambert *et al.* (1950) described the same features in cases of dermatomyositis and it is now generally accepted that there is an association between the clinical and histological features of polymyositis and electromyographic evidence of a so-called neuromyopathy (Richardson, 1956). In practice, the differential diagnosis by electromyography of a muscular dystrophy and polymyositis largely depends upon the presence or absence of these features. This is because the signs attributed to a neuropathic component are rarely found in the muscular dystrophies.

While the mechanism of the apparent denervation in polymyositis is presumably involvement of the terminal nerve fibres in the inflammatory process of polymyositis, there may well be an element of direct effect on the lower motor neurons. Evidence for this comes from those cases in which the lower motor neuron degeneration may have a mono-neuritic distribution and from others in which sensory phenomena occur. Ætiological factors in the production of muscle wasting with the electromyographic characteristics of a neuromyopathy include carcinoma, adrenocorticosteroid therapy, in particular with triamcinolone (Williams, 1959) and thyrotoxicosis. An additional observation is that involvement of both neurons and muscle fibres occur most often in the most acute cases and indeed one is tempted to suggest that this is the important factor in the production of this type of reaction. Finally, it is relevant to emphasize the functional interdependence and anatomical proximity of various parts of the motor unit, for if one recognizes this it is perhaps little wonder that some primary disorders of muscle fibres produce electromyographic evidence of an accompanying disturbance of the lower motor neurons.

In summary, therefore, electromyographic techniques are able to detect muscle fibre lesions when dysfunction of those fibres renders them unable to contribute to the integrated motor unit potential. Some differentiation of such myopathies derives from more elaborate electromyographic techniques. In particular, the finding of a systemic defect of motor end-plates in myasthenia forms the basis of a diagnostic test. It also appears to indicate a fundamental abnormality of the end-plates in this disorder, possibly constitutional, such that they react abnormally to depolarization by the subsequent production of competitive inhibition neuromuscular block. In other acquired myopathies,

electromyographic investigations have defined a reaction characterized by the presence of signs which probably indicate both muscle fibre and lower motor neuron degeneration. This particular reaction—the neuromyopathy—arises from various insults and seems to be related not only to inflammatory changes in the muscle, but also to the acuteness of the lesion.

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Dr. S. Nevin (London):

Value of Muscle Biopsy

Muscle biopsy has continually proved of value in diagnosis since Duchenne reported its use in 1872, but it has limitations. First, the sample taken may not show changes present elsewhere in the muscle, a difficulty being overcome to some extent by the use of modern electrical techniques to detect damaged muscle fibres. Non-specific pathological changes are not infrequently found in muscle of patients dying of various unrelated diseases but this is less likely in biopsy specimens and I have not seen such changes in many random muscle samples, taken at operation, from patients without systemic or arthritic disease. More important is the possibility that the changes found in a small piece of muscle may give an inadequate or misleading picture of the disease-process as a whole. Finally, there is the difficulty of interpreting well-marked pathological changes because the muscle fibre reacts in a somewhat similar manner to different kinds of injury. In this regard, it is stated by Greenfield *et al.* (1958) that no single change has been found to be specific for any disease and even combinations of changes are no more than highly suggestive.

It is desirable, therefore, that classification of muscular disorders should only be based on a full clinical history and post-mortem examination and that deductions from biopsy studies should only be tentative and carefully related to all previous study if confusion is to be avoided. It seems very probable, however, that newer techniques, such as intra-vital staining, tissue culture, new histochemical methods and electron microscopy will add greatly to the value of a muscle biopsy examination and will enable different kinds of pathological change in the muscle fibre to be identified earlier and with more certainty. Unfortunately this has not yet happened and these techniques do not answer the problems raised in this discussion. Here some confusion may exist as to the meaning of such terms as "focal restricted myositis", "menopausal muscular dystrophy", "necrotizing myopathy" and "pseudomyopathic polymyositis", due to the difficulty of interpreting biopsy findings. A wide range of pathological changes occur, for example, in cases of progressive muscular dystrophy. The atrophy and loss of fibres with fibrosis and fat replacement are commonplace as are the dystrophic changes. That granular, vacuolar and hyaline degenerative changes occur in the muscle fibre in this disease is also well known, but that this breakdown of the fibres can be acute, even necrotic, and provoke a local cellular and histiocytic response, is sometimes neglected, although it is well illustrated by Greenfield *et al.* (1958) under the title "floccular changes". Fig. 1 shows such changes in the long extensor muscles of the left thumb of a woman aged 25 with an eight-year history of

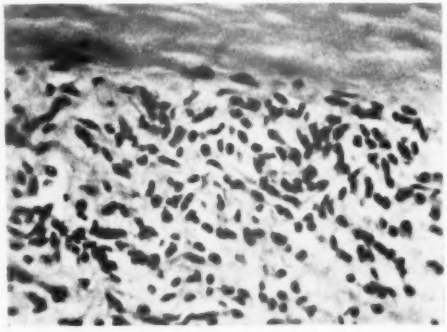

FIG. 1.—Muscular dystrophy; local round cell and histiocytic reaction associated with degenerating muscle fibres. Iron hæmatoxylin and Van Gieson. × 240.

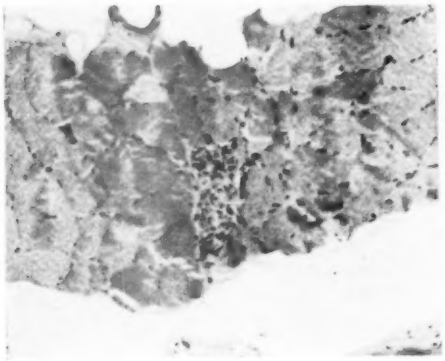

FIG. 2.—Muscular dystrophy; focal degeneration of muscle fibres with cellular response. Hæmatoxylin and eosin. × 90.

muscular dystrophy, facio-scapulohumeral in type. Loss of the movement of extension of the thumb rapidly developed, associated with aching in the dorsum of the forearm. Fig. 2 shows similar, but less acute, changes in a child of 9 with early muscular dystrophy and they are frequently found in autopsy material of this disease.

The first clinical and pathological problem is to determine the nature of cases such as the following: Bramwell (1922) described 2 patients with weakness and wasting of the quadriceps muscles. The first was a female of 53 with symptoms for one year and the second a man of 59 with symptoms for six years. In the latter the biceps femoris muscle could not be demonstrated and the brachioradialis muscle was absent on both sides. Bramwell regarded his patients as suffering from a localized form of myopathy in the strict sense. Denny-Brown (1939) described a similar condition in a woman of 42 with a five-year history. A biopsy from the right vastus internus showed enlargement of muscle fibres, many with central nuclei, but also isolated muscle fibres, completely broken down, with a great increase of nuclei, scattered throughout the fibre. He regarded the case then as a form of late myopathy but Adams, Denny-Brown and Pearson (1953) label such cases as myositis. It is clear that these cases of Bramwell's and Denny-Brown's are examples of a muscular disorder which may remain localized for a long time but is likely to progress in later life, if very slowly; other cases with mainly proximal weakness of the limbs may develop in later life without evidence of early localized atrophy. A male aged 57, under the care of Dr. Raymond Hierons, is another example of the same clinical picture. He has complained of weakness of his legs and trunk for only three years but on questioning he will say that he has been slowing up for nine years and that at the age of 30 it was noticed by others that he was not using his right leg properly. Fig. 3 shows the severe wasting of the quadriceps. Also, the lower part of the pectoralis major had almost disappeared and the lower part of the trapezius was weak but not the upper part (Fig. 4).

The biopsy findings from the leg muscles, kindly lent to me by Professor P. M. Daniel, show in one place general enlargement of the fibres with central nuclei and ringed fibres but in another focal breakdown or death of the fibres with sarcolemmal proliferation and histiocytic response (Figs. 5 and 6).

If Fig. 6 is considered alone, the condition could easily be labelled a form of myositis but,

FIG. 3.—Wasting of the quadriceps muscles in late muscular dystrophy.

FIG. 4.—Absence of lower part of the pectoralis major muscle (same patient as Fig. 3).

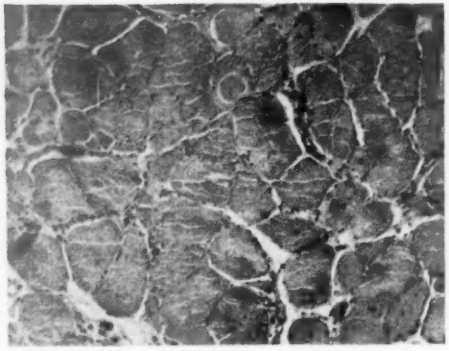

FIG. 5.—Biopsy right calf muscle (same patient as Figs. 3 and 4). Enlargement of fibres with central nuclei. Hæmatoxylin and eosin. ×90.

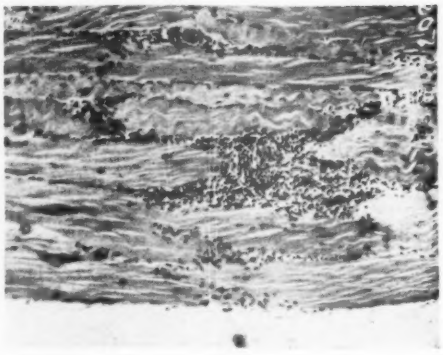

FIG. 6.—Biopsy right quadriceps muscle (same patient as Figs. 3 and 4). Focal degeneration of muscle fibres with round cell and histiocytic reaction. Hæmatoxylin and eosin. ×90.

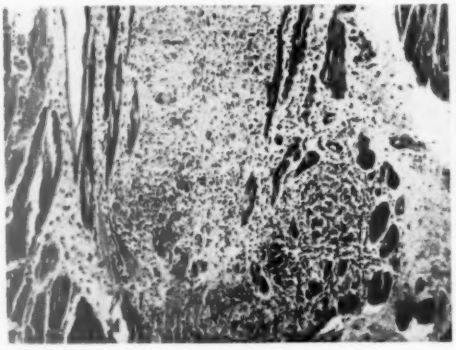

FIG. 7.—Sarcoid myositis; typical lesions. Hæmatoxylin and eosin. ×70.

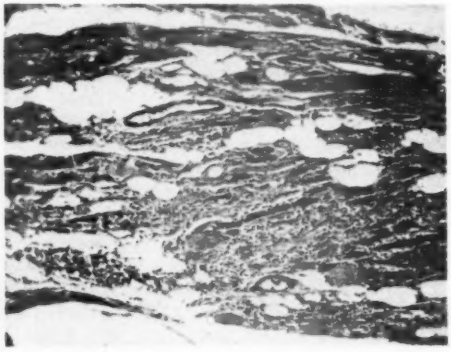

FIG. 8.—Chronic progressive myositis; diffuse cellular infiltration and degeneration of muscle fibres. Hæmatoxylin and eosin. ×70.

viewing the whole story, clinical and pathological, including the fact that he has a brother similarly affected, it is clear that this lesion is a local reaction to breakdown of the muscle fibre, a view which any pathologist would be prepared to accept, and that it is only an accentuation of a pathological feature occurring in other types of muscular dystrophy to which group of disorders I think these cases must belong. Perhaps isolated and intermittent breakdown of single or small groups of fibres is to be correlated with the slow progression and limited distribution of the disease in some of these patients, although slow progress can occur in all types of muscular dystrophy, early and late, where other pathological changes are predominant. The complete disappearance of a section of a muscle in this patient, probably by fat replacement rather than the development of contracture, is noteworthy.

This is to be contrasted with myositis where contracture of the most affected muscle and not of the stronger and over-acting muscles is the rule rather than the exception, at least in the chronic progressive case, although localized wasting can occur without contracture in this group of diseases. Other examples of a similar type of lesion could be shown in the left hamstring muscle of a woman of 50 with a ten-year history of progressive weakness of the arms and legs, although slight symptoms were noted in the second decade of her life.

More florid lesions which could be of similar nature have been described in a patient who died at 72 from some abdominal complaint after a twelve-year history of progressive myopathy (Nevin, 1936). No autopsy was obtained and I do not know of any detailed autopsy study of these late progressive muscular dystrophies.

It seems wise, therefore, to use no new names

such as those mentioned above for any of these cases without further knowledge; the title "late proximal myopathy", as used in Greenfield's "Atlas", would appear adequate to cover both the focal and more widespread cases, if the term "dystrophy" is not considered acceptable in the absence of autopsy study.

The question now arises whether these cases can be differentiated from those of chronic progressive myositis, the pathological changes in which are many and variable, and which for a long time may resemble muscular dystrophy. I think they can.

Perhaps the most slowly progressive condition of this type is the sarcoid-like myositis illustrated in Fig. 7. It is from a case, seen through the kindness of Dr. W. H. McMenemey, lasting seventeen years. Harvey (1959) described one going on for twenty-five years. Here the typical sarcoid lesion with its true foreign body giant cell and its more diffuse infiltration between the fibres seems distinctive. No sarcoid lesions were found outside the muscles in this patient at autopsy.

In Fig. 8, a biopsy from a case of progressive myositis lasting eight years, the small fibres and the diffuse inflammatory infiltration of the interstitial tissues appear on the whole different from the dystrophic lesion. There is no evidence of a gradual transition between late progressive dystrophy and the different forms of chronic progressive myositis in all their variety; difficulties in diagnosis must arise in certain cases, for reasons already given, but these will be resolved by fuller clinical and, if necessary, repeated biopsy study. In the rare cases where changes seen on biopsy are difficult to interpret, the clinical picture may be distinctive and *vice versa*. There is here no barrier to research. If some, because of the sharp focal reaction seen in some of the late dystrophies or late proximal myopathies, will seek their explanation by tissue culture and immunological studies in an autoimmune reaction, a pathological mechanism which may underlie different forms of nonspecific myositis, this is well. Perhaps such studies will open a new chapter in the pathology of muscle but I am not hopeful that the late proximal myopathy cases will be found in this category nor, judging by the recent letter in *Nature* by Pearse and Dubowitz (1960), is it likely to be easy to find a simple chemical mechanism underlying any muscular dystrophy, the problem being possibly a chemical biological one of great complexity.

Shy and McEachern (1951) introduced the term menopausal muscular dystrophy because they considered the cases they described, which resembled in general the clinical picture of a progressive muscular dystrophy, were amenable to treatment by vitamin E and cortisone. There is, unfortunately, no increasing evidence that there is such a group of cases. No follow-up studies of Shy and McEachern's cases have been published. The cortisone effect appears to have been definite but ceased immediately the remedy was stopped and possibly did not alter the course of the disease. Balchum and Towbin's case of menopausal muscular dystrophy, reported in 1952, looks very much like a myositis, while Kaeser (1958) gives so little data about the cases labelled "menopausal muscular dystrophy" that his paper cannot be taken as furthering the conception of this entity. No autopsy studies have been made but, considering the pathology as described by Shy and McEachern, some of their cases could be simply late progressive muscular dystrophies. Girard *et al.* (1959) describe a case of quadriceps atrophy coming on quickly in a woman of 20 during pregnancy which, because of the family history of possibly similar muscular disease and the histological changes, must belong to the muscular dystrophy group. Yet he is convinced of the considerable improvement produced by prednisone.

If there is no clear therapeutic, pathological or clinical basis for the entity "menopausal muscular dystrophy" the term should be abandoned to avoid confusion. The cases which are so called are either late muscular dystroph, or, more commonly, chronic progressive myositis, or some other condition such as diabetic neuropathy.

The important idea of Shy and McEachern that a direct chemical abnormality must underlie some myopathies appears, however, to be true in other instances. The most interesting of these is the chronic myopathy with a glycogenolytic defect in the muscle, first described by McArdle (1951). A striking clinical feature is that moderate exercise results in prolonged painful muscular cramps and transient myoglobinuria. This is associated with failure of glycogen breakdown in the muscle, possibly due to impaired phosphorylase activity, and there is an absence of the usual rise in blood lactate on muscular contraction. There is an accumulation of glycogen in the muscle, necrosis and phagocytosis. The patient described by Schmid and Mahler (1959) was 54. Up to 20 years of age he complained only of fatigue, between 20 and 40 painful cramps were severe and after 40 wasting and weakness of the proximal muscles set in and the quadriceps was severely affected. As there appears to be a familial incidence of the disease,

it is interesting to speculate whether dystrophy or chemical abnormality is the primary abnormality.

Because of the fibre necrosis in this disease it has been suggested that late muscular dystrophy may be associated with a chemical abnormality of a similar order. This is a valuable suggestion for further investigation but it is probably best not to introduce any new names such as "necrotizing myopathy" until more information is available.

I do not know if there is any relationship between this disease and other myoglobinurias with or without muscular dystrophy but it seems distinct from glycogen storage disease which is well known to cause myopathy in children. A case showing that glycogenosis can cause proximal myopathy in adults was recently described by Holmes and Woolf. The illness lasted ten years, from 21 to 31, and again the quadriceps was severely affected. The biopsy, on which alone the diagnosis was made, showed the presence of a neutral mucopolysaccharide, either in masses in the centre of the fibre or under the sarcolemma or throughout the whole fibre.

In the other chemical or endocrine myopathies referred to by Sir Russell Brain the biopsy findings are not very distinctive and for the most part non-specific. In many instances of thyrotoxic myopathy only some degree of atrophy may be present. The fatty infiltration of Askanazy, hyaline degeneration and floccular change are inconstant so that differentiation of this condition from myositis would appear easy from the biopsy, should this be necessary on clinical grounds.

The same non-specific changes are found in steroid myopathy and that described in Cushing's syndrome and it seems clear that much biochemical rather than histological work will be necessary to make clear the mechanism of disturbed muscle function in all these cases.

Acknowledgments.—It is a pleasure to thank my colleagues Dr. W. H. McMenemey, Professor H. A. Magnus and Dr. B. S. Cardell for their help and also Dr. M. Kremer and others already mentioned who have so kindly given me access to their cases and preparations.

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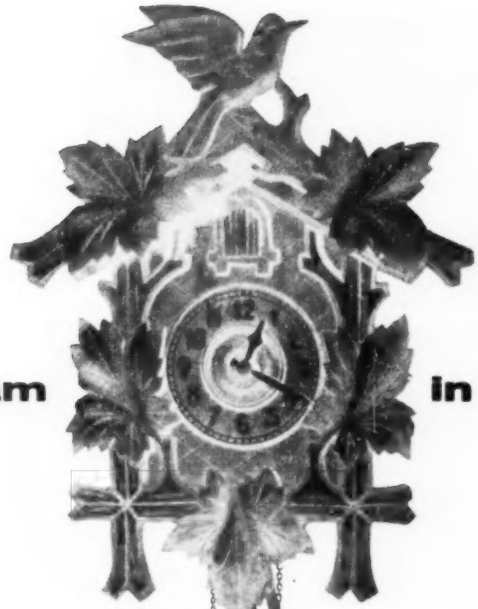

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DISCUSSION ON THE TREATMENT OF VARICOSE VEINS IN PREGNANCY [*Abridged*]

Dr. H. Payling Wright (London):

Pathology and Incidence

Ætiology.—The primary ætiology of varicose veins is still obscure though it seems certain that it is associated with the upright gait adopted by man. Blood is normally propelled from the lower limbs by means of three distinct but interacting mechanisms: firstly, by *vis a tergo*, or pressure transmitted from the arterial tree through the capillary bed to the venous side; secondly, by the massaging action of the leg and thigh muscles during movement; and thirdly, the least important for the lower limbs, by the respiratory pump. In the resting position blood return from the legs is mainly brought about by the *vis a tergo*, and this can only be fully effective when the valves, situated at the junctions of venous channels and at spaced intervals in their lengths, are functioning normally. It is well known that even when the valves are unimpaired, the flow of blood is slowed in the lower limb when the subject is upright. As the column of blood passes the "check point" of each valve, it is normally supported so that gravitational effects are reduced to a minimum. Where the valves are imperfect, or when no movement is performed by the muscles, pressure in the leg veins becomes increased and is undoubtedly favourable to the development of varicosities.

Though gravitational forces are, no doubt, of importance in the ætiology of varicose veins, it must not be forgotten that a raised venous pressure in the lower limbs may be caused by any obstruction to the upward flow of blood from them. A raised intra-abdominal pressure may well prove to be of great importance in venous dilatation and hence in the appearance of incompetent valves and varicose veins. Such obstruction may be consequent upon an overloaded colon (Cleave, 1960), an abdominal tumour or a gravid uterus (Payling Wright *et al.*, 1950).

Incompetent valves may, moreover, be consequent upon the development at some earlier date of an inflammatory thickening of the vein wall. Such fibrous replacement may follow phlebitis, or the local obstruction caused by thrombosis. In both these conditions the valves may be partly or wholly destroyed so that varicosities become established.

Two further points must be borne in mind in discussing their ætiology. First, there may well be a genetic component which is at present ill worked out—varicose veins are so common, that practically every patient can show a family history of them and this makes it difficult to establish the importance of any hereditary connexion. Second, hormonal factors are almost certainly involved, though here again there are few experimental or clinical data available on which to base such an assumption.

Pathology.—The drainage of the superficial areas in the legs is normally inwards towards the deep venous channels through a series of perforating veins, the efficiency of which is maintained by the valves. When these fail, high pressure is transmitted peripherally from the well-supported deep vessels to the poorly supported, thin-walled, superficial ones whose muscular coats are often irregularly and ill-developed. Increased intraluminal pressure causes passive dilatation and this is followed by a compensatory increase in the fibrous tissue components of the media. As back pressure continues and dilatation is maintained there follows a disruption of the elastic and muscular elements of the media. Consequent on this loss of musculature the responses of the vessel to vaso-active stimuli are impaired, and vaso-constriction becomes virtually impossible. Thus a vicious circle is set up. Finally, the vessel becomes tortuous and the surrounding tissues become fibrous and thickened irregularly, thus giving little support to the now much distended vein whose saccular lumen the valves are quite unable to occlude.

This failure of peripheral drainage of venous blood in varicose subjects can be well demonstrated experimentally by the injection of radioactive sodium chloride solution into a vessel on the dorsum of the foot. The rate of flow in the average normal person is about 2·5 cm/sec (Payling Wright and Osborn, 1952), whereas in the varicose patient it may be as slow as 0·5 cm/sec. These findings are in agreement with absolute pressure measurements made by cannulating the dorsal vein of the foot (Walker and Longland, 1950; Pollack *et al.*, 1949). The delay

in blood flow is probably in part dependent upon the pooling of blood in the varicosities, and after the injection of a tracer isotope into the vein, pockets of radioactivity can be detected in the saccular dilatations of varicose veins for as long as twenty minutes after the injection. Such findings suggest that eddies are formed at these sites, which, although allowing a continuous stream to pass, yet impede the linear flow which is normally characteristic of circulating blood.

Data from varicose vein clinic.—For about eight years I have been in charge of a varicose vein clinic attached to the Antenatal Department of University College Hospital. Here I personally see any women whom my colleagues in the obstetric clinic think might benefit from advice or treatment. Such cases include all those who complain of varicose veins, those who give a history of thrombosis or phlebitis in the past, and those who are found, on routine examination, to have varicosities. In this way I see about 9% of all the women who are booked for antenatal care in our hospital. On the average, I see each woman two or three times in order to check progress, assess any deterioration and finally, in the postnatal period, to determine whether surgical treatment should be undertaken before another pregnancy is embarked upon. It is a sad thing to see so many young women with painful and unsightly legs, and the figure of 9% from my clinic is certainly an underestimate of the situation, as I only see the worst cases and less severe ones are undoubtedly overlooked in the antenatal clinic where the women are often examined only in the recumbent position. A more realistic picture would be obtained if we recognize that about one in seven of all women during child bearing show defective veins in the legs.

I have broken down the figures from my clinic to show the incidence of varicose veins by parity (Table I). I wish to stress, however, that these

TABLE I.—NUMBER OF CASES WITH VARICOSE VEINS BY PARITY

Parity	No.	%
0	230	34
1	235	34
2	105	15
3	60	9
4 or more	56	8
Total	686	

figures are of little value in showing the true prevalence of varicose veins in multiparous women throughout the country. Our clinic receives a predominance of women having their first child and also those with obstetric abnormalities, so the numbers are heavily weighted in favour of the first group. What, perhaps, is more enlightening is Table II which shows the time of onset of varicosities as far as I am able to assess it. Even allowing that some of the parous women may first have developed varicose veins in a previous pregnancy, it is most striking how many—526 out of 686—recognized that they had defective veins before the beginning of this gestation. Of those, too, who appeared to develop them during the first three months, I am sure a considerable number already had them, although I was unable to obtain a sufficiently definite past history to confirm their presence. The greatest number which develop during pregnancy first appear during the second trimester and at the time when slowing of the blood flow in the legs is becoming most pronounced. Varicosities which develop for the first time late in pregnancy are comparatively uncommon, but when they do occur they appear very suddenly, often within a week, and are frequently associated with considerable aching pain and subjective heaviness of the legs. It is as though the muscular laminæ in the media of the veins rapidly fail over a considerable length, and the whole becomes suddenly and grossly distended.

TABLE II.—NUMBER OF PATIENTS IN CLINIC PRESENTING WITH VARICOSE VEINS DIAGNOSED

	No.	%
(i) Before present pregnancy	526	76·7
(ii) Present pregnancy:		
(*a*) First trimester	45	6·6
(*b*) Second trimester	110	16
(*c*) Third trimester	5	0·7
Total	686	

Both legs are affected in about 50% women and usually the time of onset is approximately the same for both right and left leg. Table III shows the

TABLE III.—DISTRIBUTION OF VARICOSE VEINS

Site	No.	%
Right leg only	187	27
Left leg only	169	25
Both legs	318	46
Vulva	138	20

numbers presenting with varicosities in various sites. The usual predominance of left over right legs does not appear in my series and the two sides are the same. What is of importance is the high incidence, 20%, of women who manifest varicosities of the vulva. These are usually associated with those in the legs, but are present in only a small number of women with no involvement of other veins. Vulval varicosities may be comparatively trivial and appear as a single node, often on the margin of the labium major, which gives little or no trouble and which goes immediately after delivery. Others are more severe and of such bulk that they cause great discomfort and pain. They may be so pendulous that they are rubbed and nipped in walking and are, moreover,

intolerable when sitting. Such varicosities are often associated with pruritus and they can drive the unfortunate woman nearly mad with irritation and pain. These veins disappear rapidly after delivery, but though they seem to recede satisfactorily they always reappear in any following pregnancies with a more widespread distribution and earlier in the gestation. They cannot, therefore, be assumed to be cured in the puerperium.

A proportion of cases in the Obstetric Hospital have developed thrombotic complications in the ante- or post-natal period (Table IV). These have

TABLE IV.—NUMBER OF PATIENTS WITH ANTE- OR POST-NATAL THROMBOSIS IN TOTAL GROUP STUDIED

	No.	%
Superficial veins ..	57	8·3
Deep veins	12	1·7
Pulmonary embolus ..	5	0·7

been, as might be expected, in greater numbers in the group attending the clinic than in those who showed no abnormality of the veins during pregnancy. Among the 686 women in the clinic, there was an incidence of about 10% who showed thrombosis or phlebitis, though fortunately most were of so minor a character that they did not require treatment, and did not prolong the patient's stay in hospital. Of the 5 with pulmonary embolus, none died, and indeed 4 were of so indefinite a picture that diagnosis was only made after X-ray examination suggested the presence of a typical shadow. Over the five-year period under review, I venture to think that our record of one pulmonary embolus a year is a reasonably good one.

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Mr. Harold Dodd (London):

Surgical Aspects of Varicose Veins in Pregnancy

Formerly, varicose veins and piles in pregnancy were untouchable, because their treatment was considered dangerous, and as they subsided after parturition, mothers were advised to lie up! In 1946 a woman 6½ months pregnant was seen, incapacitated by varicose veins of her left leg. As she had a family, it was imperative to carry on. She implored help. A St. Mark's Hospital surgeon told me that piles in pregnancy were injected or excised, and if the bleeding points were secured and the piles completely removed, the treatment was effective. Why should varicose veins in pregnancy bleed or recur if the principal leaking vein and cut vessels were securely ligated? A saphenofemoral ligation and retrograde sclerosing injection were done, the varicose long saphenous vein was huge, but otherwise the same as that of a non-pregnant person. The mother was relieved and the birth was successful.

Since then, operation has been done for those really needing it. Obviously only women in difficulty from their veins see a surgeon, so the paramount indication for operation on varicose veins in pregnancy emerges, that of real embarrassment and incapacitation. Other factors are the necessity for the mother to work until parturition, the impossibility of her lying up, inadequate relief by bandages and stockings and the inability, due to various commitments, to have the operation after the baby is born. Operation is now offered until the 30th week, but after this, palliation and rest are advised.

I find that vulval varicose veins are rarer than varicosities of the limbs but are often associated. Vulval varices are embarrassing, grotesque and unsightly, and their bulk and tension make walking, standing and sitting painful. The first such patient was seen six years ago and her pregnancy was eased by ligation of veins at the lower border of gluteus maximus. Dr. Payling Wright and Professor W. C. W. Nixon asked me to see a patient whose labial veins filled from the internal abdominal ring, i.e. the veins of the round ligament were varicose. She was relieved by their removal.

The Anatomy of Varicose Veins in Pregnancy

Four venous systems are affected, three of the lower limbs and those of the round ligament from the labia majora.

In the leg the long and short saphenous veins and the peripheral tributaries of the internal iliac vein may be varicose.

In my series the long saphenous vein was varicose in 63 of 67 women, the short saphenous in 3, the internal iliac veins once, and 6 had varices of the round ligament and of the long saphenous vein.

The long saphenous vein runs from the inner ankle up the leg and thigh to the foramen ovale where it enters the common femoral vein. It has 2 groups of tributaries, the peripheral and the inguinal. The peripheral consist of 2 in the thigh and a pair from the leg; one or all may be varicose. The groin group consists of 4 vessels, and 2 are notable in pregnancy, the superficial external pudic vein and the deep external pudic

vein, which joins the saphenofemoral junction inside of the foramen ovale, and is easily overlooked. These 2 vessels drain the mons veneris, labia majora and upper inner aspect of the thigh. They may be greatly dilated, and for a cure they must be divided from the varicose saphenous vein.

The short saphenous vein proceeds from the outer foot and ankle to the popliteal space and usually empties into the popliteal vein, it is varicose but one-seventh as often as the long saphenous vein.

The internal iliac vein.—The peripheral tributaries of the internal iliac vein, the pudendal and gluteal veins may become varicose. The gluteal veins run backwards from the labia, perineum and upper inner thigh under the lower fold of gluteus maximus into the pelvis. Other perineal veins join the pudendal vein in the ischiorectal fossa and so to the internal iliac vein. One such patient has needed operation.

The veins of the round ligament are normally inconspicuous. In pregnancy they can be huge and could be compared to a varicocele of the spermatic veins. Either side may be affected. They drain the labia majora and converge into the inguinal canal through the internal abdominal ring into the ovarian veins.

Thus 3 sets of veins may enlarge the vulva—the tributaries of the long saphenous, of the internal iliac and of the ovarian veins. In my series, the long saphenous and ovarian veins were affected together six times.

The Diagnosis

The exact diagnosis of varicose veins is essential, as the strategic vessels are in different places, and if a wrong vein is divided no benefit will accrue.

The long and short saphenous veins.—They are proved by tourniquet tests, and an indubitable down-filling wave or cascade must be seen before any vein is pronounced incompetent.

The peripheral tributaries of the internal iliac vein.—Varicosity of the gluteal veins is diagnosed by a process of exclusion. After emptying the veins, the fingers press on the foramen ovale and internal inguinal ring simultaneously. This prevents filling by the internal saphenous and the round ligament veins. The patient stands, the veins are watched. If the internal iliac tributaries are varicose, the varices will fill. Further help is available by a tourniquet held tight in the fold of the buttock which will control these internal iliac vessels.

The vulval veins form a pear-shaped mass with the base at the posterior part of the labia majora, which is alarmingly deformed. After emptying the swelling is largely but not completely controlled by pressure with the fingers over the internal abdominal ring.

A Concept of Varicose Veins

Before discussing treatment, may I suggest a concept concerning varicose veins and their complications. It is that they arise as a result of excessive high pressure continuously distending the superficial veins of the lower limbs and vulva when the patient is upright.

Arising from this idea are four questions: (1) What is the normal pressure in the superficial veins? (2) Where does the high pressure come from? (3) How is it normally kept out of the subcutaneous veins? (4) Why do venous valves fail and allow pressure into the superficial veins?

(1) The pressure in the superficial veins is normally zero to 30 mm Hg.

(2) High venous pressure ordinarily occurs in two places: (*a*) In the deep veins of the lower limbs during movement, when the pressure rises to 90 mm Hg. This assists the venous return and is referred to as the second heart or the calf-muscle pump. (*b*) In the thoraco-abdominal cavity during lifting, coughing, straining, &c., the pressure may rise to 200 mm Hg. When the valves of the iliac or common femoral veins are faulty or absent (as occurs in 36% of normal persons) this pressure is exerted against the valves guarding the superficial veins, including the long saphenous vein, and should they fail, then the varicose-forming process starts.

(3) The superficial veins are protected from a back-flow of high pressure by the valves in the veins connecting them to the deep veins.

(4) High pressure enters the superficial veins through the connecting veins in which the valves have failed. The long and short saphenous veins are a form of such communicating veins. There is a familial tendency to varicose veins in 75% to 80% of women with them.

Valves fail after thrombosis of the deep, connecting or superficial veins, and also from continous venous obstruction.

The hormones of pregnancy, progesterone and relaxin, which dilate the uterine vessels to 30 to 40 times their normal size (Barcroft and Rothschild, 1932; Barcroft *et al.*, 1933), in some women, affect the saphenous and ovarian veins and so cause the valves to become inefficient. Varicosities appear or become worse in the first three months of gestation, before the uterus can mechanically press on the iliac veins. The women I see with troublesome varicosities are usually in the 4th or 5th month.

Implicit in this concept of continued high pressure in the superficial veins is the progressiveness of varicosities; they are not stationary, nor will they ever burn themselves out. This conditions our advice regarding palliative and radical treatment.

The Treatment of Varicose Veins in Pregnancy

If this concept of superficial venous hypertension is true, then the symptoms caused by it will be relieved if a pressure equal to that in the veins is applied continuously to the limb and/or the vulva. When the condition is slight to moderate, this pressure gives adequate relief during pregnancy. It can be given by elastic stockings and/or bandages to the limbs, and for the vulva by close-fitting robust panties. There are two disadvantages; stockings, bandages and panties are hot to wear and some patients dislike and cannot tolerate such confinement. Although women are helped until their baby is born, those whose veins were present before conception and give clear signs of valvular deficiency will worsen with time and further pregnancies. Pressure is palliative, it does not stop the leaks. Troublesome vulval varices in a non-pregnant woman are rare although unsightly, so unless they are excessive they perhaps can be treated expectantly.

When the veins are gross, operation to stop the leak of high pressure into the superficial veins is advisable and curative. Usually only one leak from the long or short saphenous vein is present. These are tied flush with the common femoral vein or popliteal vein and the saphenous trunks are stripped out. With the long saphenous vein, the superficial and deep external pudic tributaries are divided.

For the varices in the vulva, in addition to tight panties there are two remedies. The fearsome subcuticular vessels in the fringe of the labia can be injected to prevent hæmorrhage during labour. When they are gross, the inguinal canal is opened as for a hernia, the veins in the round ligament are ligated at the internal abdominal ring and the round ligament is excised. It strips out readily with the enlarged vessels from the labia majora. The enlarged tributaries of the internal iliac vein are tied at the inferomedial border of gluteus maximus.

Injections into varices.—I am apprehensive of these because the thrombosis which usually follows may spread to the perforating veins and in time make their valves inefficient. I do not think that gross veins are cured by injection. I believe injections to be uncertain in principle, dangerous locally and possibly constitutionally.

Results.—No deaths or morbidity to mother or child have occurred. One birth followed uneventfully at 7½ months, four weeks after the operation. The mothers have said the operation was worthwhile, many have had subsequent babies and several 3 more.

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Mr. W. G. Fegan (Dublin):

Continuous Uninterrupted Compression Technique of Injecting Varicose Veins

No standard treatment of varicose veins has yet been accepted. Injection therapy is in disrepute because it has been established that it is followed by recurrences which are frequently worse than the original state.

We have been using an injection technique for over ten years and have found that it is not followed by a high percentage of recurrence and that it certainly does not leave the patients worse than they were prior to treatment.

A great part of our work has been carried out on pregnant women. During pregnancy, varicose veins can produce distressing symptoms. These symptoms are relieved after one or two injections. This, in itself, makes treatment worth while, quite apart from the fact that it reduces to zero the incidence of thrombophlebitis in the puerperium.

Symptoms such as cramps in the leg, tiredness, hot throbbing pain, and constant pain in the legs are all relieved, together with the swelling, ulceration and eczema. Over a period of seven years no patient has been admitted from the Varicose Veins Outpatient Department in the Rotunda Hospital for surgical treatment. No patient has, in the last three years, attended for treatment of varicose ulcers, where, formerly, there was an established ulcer clinic.

It has been said that it is pointless treating varicose veins during pregnancy because a high percentage spontaneously recover after delivery. This may be true but, if we consider the fact that five times as many women as men suffer from varicose veins and that 4 out of every 5 women date the commencement of the varicosities from pregnancy, it becomes apparent that, if veins are cared for and controlled during pregnancy, fewer women will suffer from trouble with their veins later in life.

It is, in fact, untrue to say that a high percentage recover spontaneously after delivery; a high percentage improve but very few completely recover and many develop thrombophlebitis. It is to cases in this latter group that great attention should be paid. They appear to improve after the pain of the thrombosis has settled down.

Quietly and insidiously, the lumen of the thrombosed vein becomes re-established and, because of the added valvular injury, the pressure of the blood in this re-established vein is higher than before. In six months' or a year's time the patients in this group will find that their veins are much worse than before their pregnancy. Should these patients' legs be examined at regular intervals, these findings would be confirmed.

In order to treat varicose veins successfully, one must spend some time in studying the physiology of the peripheral pump. Briefly, in the calf muscles there is a powerful pump system which is, in many ways, analogous to that of the heart.

The principle of our treatment has been to concentrate rather on restoring the efficiency of the pump than on obliterating apparent superficial varices. In order to do this, one must be able to locate accurately the exact points of emergence of the veins with the incompetent valves because it is through these veins that blood is flowing in the wrong direction and abnormally high pressure is being transmitted. This produces the double disadvantage of high pressure in the superficial veins and reduced output from the peripheral pump.

The introduction of a sclerosant into a vein can be followed by a multiplicity of reactions, varying from a wide-spreading thrombophlebitis to minimal or no reaction.

The ideal method of achieving our aim of permanently blocking the offending leak is to produce a short fibrotic segment of vein, involving the junction area. We have observed that this can be achieved by carrying out the following procedure: (1) Selecting a vein with a good wall. (2) Introducing the sclerosant into this vein after it has been emptied. (3) Maintaining the sclerosant in the segment for 30 seconds. (4) Applying compression immediately to the site of injection, maintaining it until one is quite sure that, when the patient stands erect, the internal pressure of the blood in the adjacent unobliterated vein cannot reopen the segment.

It is important to spend some time examining the legs of each new patient and accurately marking the points where the incompetent derangement begins because one injection, properly placed, can rid the leg of a vast complex of varicose veins. We have found it of great help when attempting to locate the sites of incompetence to consider three factors: firstly, our knowledge of the normal position of the communicating channels, secondly, the pattern of the varicosities and, finally, palpation of the fascia of the leg.

If one examines a number of legs with the tips of one's fingers, one will suddenly become aware that there are weaknesses or depressions in the deep fascia. It will be found that these depressions correspond with the localized blow-out in the vein and with a known site of a communicating channel between the deep and superficial veins. Digital pressure at one or more of these points will control the filling of the superficial veins. These depressions are the sites of election for injection.

The exact steps in the process of reopening of a thrombosed vein do not appear to have been clearly worked out. From Figs. 1, 2 and 3 one can see the process of reopening which I believe to be the commonest. Fig. 1 shows the slit-like channels developing between the clot and the wall of the vein. Fig. 2 shows this process to have advanced until a third of the circumference of the vein has been involved. Fig. 3 shows the new channel to have become circular instead of slit-like and the central organized clot pushed to one side.

We believe that the process by which the lumen of this vein has become re-established is the result of a combination of three factors: (1) High pressure of the blood in the adjacent veins. (2) The development of slit-like channels between the organizing clot, which is retracting, and the wall of the vein. (3) The lack of external supporting compression.

We believe that this is the common method by which the lumen of the thrombosed vein becomes re-established and that it can take place very quickly, in fact within a few weeks of the onset of thrombosis. This phenomenon we have observed clinically on many occasions.

But, if the vein is emptied before the sclerosant is introduced and the sclerosant is maintained undiluted in a small segment of the vein for a period of time and followed immediately by uninterrupted compression, then the histological appearance of the vein is very different. This is shown in Figs. 4, 5 and 6. Here we note the absence of an organizing blood clot, the considerable endothelial peripheration and the great thickening and fibrosis in the wall of the vein.

We inject all varicose veins without selection. The commonest site of injection has been the Hunterian communicating vein (above the medial condyle of the femur). As far as we know, there have been no ill-effects from this technique or from the solution used (sodium tetradecyl). The danger of spill into the deeper veins is theoretical if the amount is kept small. On six occasions we have observed large sapheno-varices to disappear after injecting the Hunterian communicating vein. This latter observation is important with regard to the evaluation of Trendelenburg's operation. 3 patients with intermittent claudica-

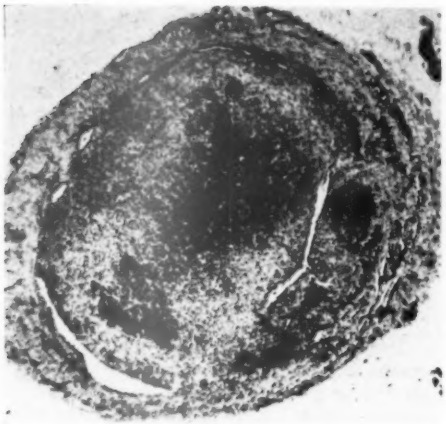

FIG. 1.—Shows the slit-like channels developing in the line of cleavage between the retracting clot and the wall of the vein.

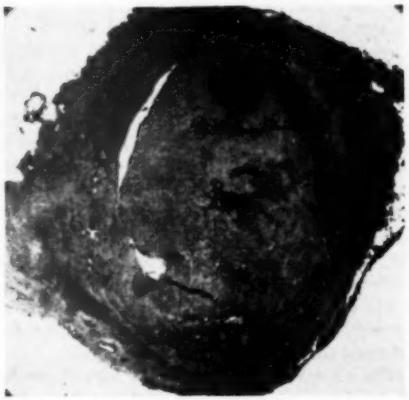

FIG. 2.—Shows a vein in which this cleavage has advanced until one-third of the circumference of the vein has been involved.

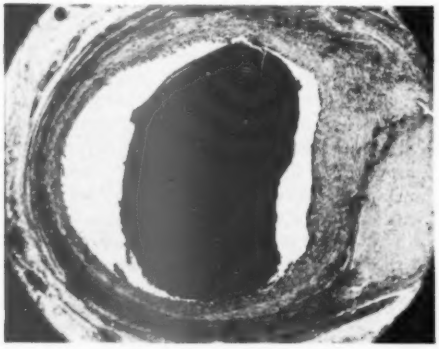

FIG. 3.—Shows the new channel to have become circular instead of slit-like and the organized clot to have been pushed to one side.

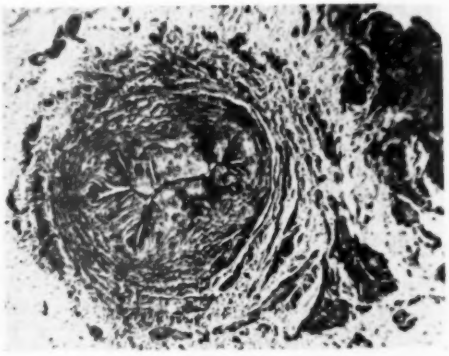

FIG. 4.—Photograph taken following the compression technique showing no organizing blood-clot and no circumferential slit-like cleavage channels.

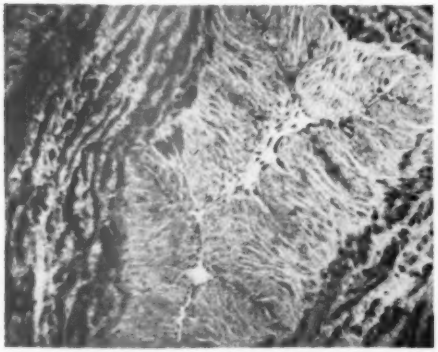

FIG. 5.—High power photograph taken of a vein treated similarly to that shown in Fig. 4.

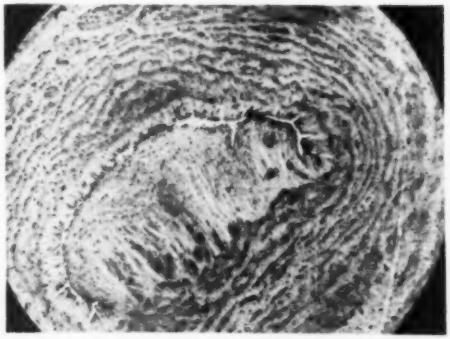

FIG. 6.—Demonstrates a case in which the endothelial proliferation is mainly unilateral with, again, no evidence of channels developing circumferentially.

tion got relief from their symptoms following treatment for their varicose veins.

People who suffer from deep vein thrombosis during pregnancy or following a fracture and who subsequently develop superficial varices are treated by us. We disregard the history of deep vein thrombosis and consider that these people require to have the leaks from their peripheral pump sealed off, more so than people who have not had deep vein thrombosis. They are suffering from the double embarrassment of diminished output from the pump and continued high pressure in the superficial veins. If the superficial veins are destroyed, there is a definite improvement in their symptoms, although the leg does not completely return to normal.

The extravascular technique which we have used in a large series of cases has been found particularly useful in treating labial varices and the large aneurysmal vascular clusters in the instep of the foot. To avoid the unpleasant reaction following the extravascular technique it is necessary to use only a small amount of the solution, to diffuse it well in the tissues, to keep it well away from the skin and to apply compression with soft rubber over the site of injection.

It is interesting to note that on many occasions we have been able, from the appearance of the patient's veins, to suggest to her the possibility of pregnancy before she was aware of it through any other symptom.

Summary.—From the experience gained and the data collected in the treatment of over 4,000 patients for varicose veins, we are satisfied that this technique of immediate and uninterrupted compression following the injection of the sclerosant into an empty vein at the site of election is well worth while. Apart from the early symptomatic relief, the long-lasting curative effect has, in our hands, been better than that following operation; the most important feature being the avoidance of extensive clot formation with the subsequent reopening of the affected vein. This can be achieved by immediately applying and maintaining uninterrupted compression at the site of injection.

Mr. Alan Curtis (Hexham):

The Surgery of Varicose Veins in Pregnancy, and its Results

In pregnancy a woman should be at her healthiest and happiest, but this desirable state is all too often marred by a variety of conditions, some unavoidable, some, as varicose veins, eminently treatable. They cause much discomfort and disability, and interfere with normal activity and *joie de vivre*, so adding indirectly to the hazards of pregnancy, quite apart from their own thrombo-embolic risks.

It is doubtful whether pregnancy actually initiates varices; they commonly date from the teens, and gross cases are common in men and nulliparous women. In most cases pregnancy does make them much worse, both subjectively and objectively, with some abatement after delivery. But any case worthy of complaint has permanently incompetent valves, and will require radical treatment sooner or later.

This being so, unless there is some sound reason against surgery, why not "sooner", with great benefit to the victim?

There are two main arguments advanced against this view: the risk of miscarriage and the effect of possible future pregnancies.

As a student I came to regard pregnancy as a somewhat precarious state, very easily upset. I soon learned how very difficult it is to disturb a healthy pregnancy in a healthy woman, except by direct mechanical or hormonal interference. I saw James Clark successfully use quinine in threatened abortion, to hurry the inevitables and settle the others. As a general surgeon I saw with what remarkable impunity one could operate in pregnancy, and was driven to the conclusion that in considering the merits of any proposed operation the risk to the pregnancy was quite secondary to the benefits to health, mobility and general well-being, and the reduction of risk which might be expected to accrue from it.

Thus in varicosities of the lower limbs, having excluded as far as possible cases of instability (after long involuntary infertility, habitual abortion, &c.) one should treat the veins strictly on merit by the accepted methods of stripping, local excision, injection and support. Most of my cases have in fact been treated in the middle trimester, mainly because they presented then.

Vulval varicosities are in a special category, possibly less common, retrogressing more completely after delivery, and with a slightly different mechanism. It is difficult to believe they do not increase the risk of pelvic venous thrombosis—some seem in danger of rupture—or constitute a handicap in delivery. They are all very uncomfortable, and most methods of support equally so. Surgery is less easy; they are embedded in vascular fibro-fatty tissue, and have stumpy deep connexions. Nevertheless, severe cases may justify ligature or excision; I never feel quite happy about injection here.

As for effect of future pregnancies, after adequate stripping gross recurrences are rare, a few injections normally sufficing, so that there is no good reason for waiting till the family is judged complete. One does of course meet the occasional patient whose ability to develop fresh

varices is phenomenal; this type seldom needs any help from pregnancy.

I cannot boast a large series; no patient has miscarried, one threatened but quickly settled, and there have been no other complications. Several have gone through further pregnancies without serious relapse, and all have been most grateful for the relief of symptoms.

I quote the two least straightforward cases as the most interesting:

Case I.—Seen September 1952: primigravida, aged 38, 20 weeks pregnant after eleven years valid marriage. Severe varicosities twelve years, tied elsewhere three years previously, and for four weeks had become very troublesome. She had the usual large bunches in the calves, but her chief complaint was of a left saphena varix the size of a cricket ball, and of large vulval varicosities. Though an elderly primigravida, I decided to operate and removed the six main groups a few days later. In her case tying the large vessels from labia to groins cured the labial varices. Convalescence was uneventful, she needed a few injections. She has failed to produce any further family, but had numerous gynæcological misfortunes, and will probably have belated stripping soon.

Case II.—Seen March 1955; sixth gravida, aged 33, severe varicose veins for eleven years, and a history of superficial thrombosis in an earlier pregnancy. She showed widespread varices throughout her legs, and very large labial veins, which appeared in danger of rupture. Her veins were stripped as far as possible, with local excision and ligature, including those in the right labium; a large one on the left, the size of the vena cava, was obliterated by oversewing. Two days later she had a slight "show", but settled with sedation. Since then she has been pregnant at least twice, and needed a few injections.

Mr. Wilfrid G. Mills (Birmingham) said that the obstetrician would be required to advise his patient as to the probability of any permanent deterioration in varicose veins as the result of any given pregnancy. The fact that the varicosities of the vulva would so constantly return to normal after the puerperium afforded some evidence that the affect of pregnancy on varicose veins was transitory. Any permanent ill-effect was due to valvular incompetence arising during pregnancy and this could be wholly avoided in the veins of the lower leg if they were adequately supported by bandaging or elastic stockings throughout pregnancy. The veins that required surgical treatment during pregnancy were precisely those which ought to have been treated before a pregnancy commenced.

Miss A. M. Dickins (London) asked why superficial veins thrombosed so early in the puerperium and deep veins so late.

Mr. Clifford A. Simmons (London) said Mr. W. G. Fegan had allowed him to examine and question 25 patients in his clinic before he saw them. The results of treatment were very satisfactory to the patients. Feelings of pressure or cramps were relieved immediately. This type of treatment seems very safe and gave such comfort to the patients that it would seem well worth while in any maternity unit, provided the time and space could be found for a vein clinic.

Dr. E. Robert Rees (London) referred to the beneficial effect of lifting the foot of the bed for nocturnal cramps. He had been practising this for four years, on the recommendation of Mr. Stanley Rivlin, with complete relief of cramps in all cases. He felt sure that careful questioning of the small percentage who did not get relief would reveal that they probably placed a pillow under the mattress or at the most a couple of telephone directories under the foot of the bed. It was essential to raise the foot at least 9 in. because only then would the calves be above the level of the heart, and then probably only just.

The one adverse reaction to this had been the development of heartburn which in any case was a common accompaniment of pregnancy. In some of these cases the precipitation of heartburn had been so closely related to this posture that he had had to say to the patient that she must choose and decide which was the more distressing, heartburn or cramps in the legs.

He considered that wholesale condemnation of garters was a mistake. They could obstruct the return in superficial veins but where there was incompetence of the thigh veins they could often prevent the full effect of regurgitation from these into the leg veins. He had now seen several patients who insisted on wearing garters because they found their legs much more comfortable.

Dr. Payling Wright, in reply, said she was not convinced that Miss Dickins was correct in her belief that there was a time difference in the onset of deep and superficial thrombosis but she had no data on that subject. If such a difference did exist, however, it might be associated with the observation that blood flow-rate in the legs was not minimal until the seventh or eighth day after confinement to bed. Only then the flow in the deep veins might be sufficiently sluggish to allow of thrombus formation. More likely was the fact that superficial veins presenting with painful, inflamed areas on the third or fourth postnatal day were unlikely to be overlooked by the patients, while deep thromboses were often silent and so were not diagnosed until considerable activity was resumed later in the puerperium.

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Section of Surgery

President—RODNEY MAINGOT, F.R.C.S.

Meeting
March 2, 1960

DISCUSSION ON ACCIDENTS IN THE OPERATING THEATRE

Dr. Keith Simpson (London):

Surgical (and dental) theatres are places where the risks that are consciously faced by the operator and anæsthetist are high—greater than ever before owing to the increasing complexity of techniques. The bottle and mask have given way to the "cocktail" trolley, cylinders are becoming replaced by ampoules and the utterly passive patient is being maintained by artificial inflation and a cold or extracorporeal circulation, whilst surgery of a delicacy hitherto undreamed of is being performed on vital parts, parts whose physiological efficiency can be maintained electrically and pharmacologically. In these things a high technical efficiency counts for much, and a sensitive operator with eyes and ears attuned for the first signs of disaster for as much again. I must ask at the outset whether the strained atmosphere of tension and the prolonged physical and mental demands made upon some teams in the theatre are the ideal working conditions most likely to avert stress breakdowns, or whether they may not conduce to fatigue and the kind of lapses of acuity of the senses that encourage accidents. A carefully integrated partnership, carefully planned for a full team of experienced theatre personnel, has one advantage that the fighting Services and industry recognize—the alert freshness that comes from periods of rest.

Definition of an accident.—There are possibly no accidents in the theatre that are, in Sir Frederick Pollock's definition, "not avoidable by any precautions that a reasonable man might take". Something somewhere has somehow at some time escaped the critical attention of some expert whose duty was to see that the risk was avoided. I am not, of course, talking of the risk of breakdown of a high œsophago-enterostomy, of the development of arrhythmia or fibrillation during cardiotomy, or of frank intolerance to synthetic cocaine derivatives. I am speaking of mistakes in the use of labelled drugs or gases, of burns, of theatre explosions, of the use of defective anæsthetic apparatus, of lack of expert vigilance, of bungling surgery, of air embolism, of many common vagal reflex disasters. These are the "accidents" we should consider, for the majority are avoidable.

Accident or misadventure—liability.—This raises a preliminary question as to whether there is any real difference between something that the surgeon or anæsthetist recognises as a natural risk of the procedure that he must take every step to minimise (though he may plead the utter impossibility of averting the risk altogether) and something unforeseen that takes him by surprise, a "bolt out of the blue", a "pure accident" (with varying degrees of purity) that, looking back, he feels might have been avoided. Some people have in the past tried to make a separate class of the natural risks that miscarry and to call them "misadventures" as distinct from "accidents", possibly in the hope that litigation may seem thereby to be held a little farther away. This is in law without foundation, for accident and misadventure are synonymous. A surgeon or anæsthetist may have to defend either on the grounds of reasonable care, and lack of such care will incur liability. But mistakes do not, provided due care is proved.

Accidents due to negligence.—I have taken from my records of the last ten years exactly 100 successive fatal theatre accidents. To go back for thirty years, as I have for other purposes, does not illuminate the issue very much, though it does exhume some remarkable practices. Accidents are no less frequent it would seem, but they are on the whole less stupid. Standards of surgical and anæsthetic practice have undoubtedly improved enormously during the last twenty years and, except for one incorrigible piece of stupidity, that of the dentist who still undertakes the combined risks of anæsthetist and surgeon, utter lack of responsibility of the indefensible kind that the amateur anæsthetist or general practitioner otorhinolaryngologist used to undertake so light-heartedly has almost disappeared, but not altogether. The wrong patient may still have his healthy femur pinned—and die of it, the man who needs anal dilatation and the woman whose shoulder needs manipulation may still be switched, 9 in. of femoral artery may still be excised in elementary error for vein, swabs and forceps may still be counted "in" instead of "out", rectal anæsthetic be put up in surgical spirit instead of saline, corrosive iodized phenol painted on the skin instead of a weak iodine solution. I am giving random cases of frank negligence from my own experience. And I cannot, of course, speak of the surgeon (or anæsthetist) whose enthusiasm exceeds his judg-

ment: of the man who, without recourse to available diagnostic methods, presses on to excise a lung tumour only to plunge his fingers into an aneurysm of the aorta, who excises a coarctation only to find himself too short of tissue to effect a better channel, of the anæsthetist who habitually gives overdoses of Pentothal to ease his responsibility to acquaint himself with adjuvant anæsthetic drugs, or who finds himself seated out of sight of his patient, muscled there by visiting surgical enthusiasts. These are not just simple accidents. They constitute near, if not altogether, criminal disregard for the reasonable safety of the patient, and they are very rare indeed.

The frequency of avoidable accident.—Accidents of surgery or anæsthesia are commonly only recognized too late—when it is not the accident but the results of it that stare the staff in the face. The time to inspect electrical apparatus, tubing, or drugs, the time to count swabs and forceps is before, not after, their use. Some accidents, like explosions, are obvious, but others, like air embolism, are easily overlooked and many are survived by the patient. Statistics must greatly underestimate the total number of theatre mishaps.

In this series of 100 cases in which something unforeseen (and which could not be regarded as a natural hazard of the procedure) ended fatally, there were 74 surgical and 26 anæsthetic mishaps (Tables I and II), nearly 3 to one on the surgeon

TABLE I.—100 OPERATIVE/ANÆSTHETIC ACCIDENTS
Surgical—total 74%

Negligence		5
Transfusion errors		3
Accidental hæmorrhage		34
Operative breakdowns	8	
Post-operative breakdowns	5	
E.N.T. procedures	13	
Needle explorations	4	
Instrumental tears	4	
Vagal inhibitory reflex		17
Surgical	9	
Anæsthetic	8	
Air accidents		15
Surgical procedures	8	
Transfusion	3	
Medical procedures	3	
Obstetric procedures	1	

TABLE II.—100 OPERATIVE/ANÆSTHETIC ACCIDENTS
Anæsthetic—total 26%

Negligence		2
Obstructed airways		12
Vomit inhalation	5	
Foreign body inhalation	2	
Mucus/blood/pus, &c.	4	
Laryngeal spasm	1	
"Excess" anæsthetic		8
Pentothal	5	
Cocaine	2	
Spinal procaine	1	
Explosion		1
Anaphylactoid reaction		3
Penicillin	2	
Tetanus	1	

having to take any blame that might be attached. It is no surprise that many surgeons have come to regard every patient as a potential litigant, but it is not perhaps entirely to his disadvantage that he should do so.

Of the surgical accidents other than those due to frank lapses of care, nearly half were due to hæmorrhage that was not envisaged and certainly should not have been fatal. Of these about a third ensued upon E.N.T. procedures, and I cannot emphasize too strongly the surprise or even frank incredulity that greets the finding of blood in the airways after nose and throat operations. A trickle of warm blood from a tonsillectomy can be quietly but surely fatal during the few post-operative hours, especially in a sleepy or narcotized infant under the care of a night ward staff. Only constant nursing attention can avert these tragic deaths. Of the remainder, needle biopsies, especially of the sternal marrow, are particularly hazardous, for there is little room for manœuvre. It is a surprise that more paracentesis procedures, especially in the chest, are not followed by dangerous bleeding from either intercostal or lung vessels.

Of the remaining surgical "accidents" two groups are particularly common: vagal inhibitory reflexes and air embolism (*see* Table I).

In a series of 87 vaso-vagal inhibition deaths I studied from my general records several years ago the sources were, in decreasing order of frequency: obstetric 19, serous membrane 18, throat or glottis 17, bladder and urethra 13, carotid sheath 9, skin 4, cardiovascular 3, alimentary (viscera) 3, peripheral nerve 1.

Not all of them were in anæsthetized subjects, and indeed no patient is likely to have been effectively anæsthetized for this virtually eliminates the possibility. A high emotional tension, fear or fright undoubtedly heightens the risk. In one case a young man, in mortal fear of another chest needling, said to his father "if they do it again I'll die"—and he died the moment the needle entered the chest wall, before anything further had complicated the issue. In another, an anæsthetist warned a surgeon that each time he lifted the vagal sheath during his dissection of the thyroid the pulse rhythm changed. A final tug on it during mopping up in the operative bed was instantly fatal. Most of the operative cases occur in the last phases as anæsthesia is lightening when the risk of a vagal reflex is either forgotten or taken to be too small to matter.

Air accidents have only come to be accepted as dangerous since the last war when pressurized blood administration became more popular, and fatalities drew attention to the importance of air-tight joints, sound rubber and a clean technique. Operative procedures near venous sinuses are particularly liable to air embolism, most of all facial sinus and nuchal operations, but any open vein will suck air under the right conditions,

and diagnostic or therapeutic injection of air, the induction of a pneumothorax or pneumoperitoneum, or vaginal and tubal insufflations, all provide occasional fatalities. We do not know how often they are fatal, for many are naturally overlooked.

Anæsthetic accidents provided 26% in this series (Table II). Explosion is, fortunately, rare: out of 36 cases—one in every half million major anæsthetics investigated by the Stead Committee (H.M.S.O. 32–436)—almost exactly a half were due to static discharge. The old bogy of an obstructed airway from vomit, bitten-off tube, dental swab, teeth, blood, or, more fortuitously perhaps, from laryngeal or bronchial spasm is the main source of death. No effective means of clearing an airway blocked by fluid has yet been devised, and even when it is temporarily effective, fulminating infection often follows or a residual lung abscess remains to identify the error.

I have referred above to vaso-vagal arrest of heart beat and respiration, and some 20% of that series were in fact due to passing or withdrawing airways or instruments from the glottis or larynx under ineffective anæsthesia. When difficulties occur in anæsthesia, they are as likely as not to have ensued because they were noticed too late. Bad choice of anæsthetic and overdosage are signs of inexperience or stupidity, and neither is frowned upon by the law. Indeed, on appeal in a recent case it was held that an anæsthetist could not be held negligent because he had not kept up to date with his reading, and was in consequence uninformed on a risk attaching to what he did. This is a matter of competence and not of negligence.

Hypoxia or anoxia as a cause of cardiac arrest and death is a result, and not a cause, of accidental happenings in the theatre. It is yet another example of turning to the stable door after the horse has bolted—a fatal attitude to take over "accidents in the theatre". The best way to avoid them is to anticipate them, and plan to avoid them.

Mr. J. P. Mitchell then spoke on *Diathermy Accidents* (*see Proceedings*, **53**, 348, May 1960).

Mr. B. B. Milstein (Cambridge):

Cardiac Resuscitation

Cardiac arrest in the operating theatre is an emergency which may occur in any branch of surgery and appears to be increasing. Thoracic and cardiac surgery account for only one-third of the cases. The incidence of cardiac arrest is difficult to determine but is probably about 1 in 3,000 operations. Figures which I have obtained from the Registrar-General suggest that about 600 cases of cardiac arrest occur in this country every year (Milstein, 1956). This is probably an underestimate and in order to obtain further information a cardiac arrest registry to which all cases are reported should be established. In published series of cases of cardiac arrest, the mortality is 70–90%, as it was fifty years ago (Milstein, 1956). In 1,700 recent collected cases the mortality was 71% (Stephenson, 1958). One of the tragedies about cardiac arrest is that it commonly occurs in otherwise healthy patients. The highest incidence is in the first decade of life which accounts for 24% of all cases. 60% of patients are under the age of 50.

The brain will withstand complete anoxia for about three minutes. The immediate objective in dealing with a case of cardiac arrest is not to restart the heart, but to restore the supply of oxygenated blood to the brain. This must be done within the vital three minutes available. Restoration of the heart beat can be done subsequently at leisure.

To ensure success in the treatment of cardiac arrest one must have a rigid rule of diagnosis. The rule is that if during the course of any operation or procedure under local or general anæsthesia the patient's general condition deteriorates, one must feel for the pulse in a large artery. If the abdomen is open, the abdominal aorta or one of its branches can be palpated. If it is not, the carotid artery in the neck should be sought. If the pulse cannot be felt the chest should be opened, the diagnosis confirmed by inspection and cardiac massage started immediately. It is often protested that this is a very drastic course to adopt. But one is dealing with a very serious condition, and the patient will die or suffer serious neurological damage if the blood supply to the brain is not restored within three minutes. The second objection raised is that one might open the chest and find the heart still beating. This can hardly be regarded as a very serious objection for the risk of a thoracotomy is slight. In the 12 surviving patients out of 14 that I have personally treated, in whom the chest had to be opened for cardiac massage and in whom no aseptic precautions were used, there was no case of subsequent infection. Of course, antibiotics were used freely. Even though the heart is beating cardiac massage may still be required because the cardiac output is inadequate. Patients can develop neurological damage and die from a low cardiac output with a heart beating inefficiently as well as when the heart action has ceased completely.

An electrocardiogram is of little value. Usually an electrocardiograph is not available, so that the question of its value does not arise, but even if it is it may not be helpful and can be misleading. It can be helpful to the anæsthetist in giving him

warning that cardiac distress may occur when he sees the presence of an arrhythmia, but a reasonably normal tracing can be obtained when there is no visible mechanical contraction and the patient is dead (Reynolds, 1953). One is not really interested in the electrical activity of the heart but in the cardiac output or the blood pressure, and these can now be monitored continuously during an operation.

In the treatment of cardiac arrest two things are necessary to supply oxygenated blood to the brain. One is ventilation of the lungs and the other is cardiac massage. When this emergency occurs, therefore, the anæsthetist must stop administering all anæsthetic agents, and inflate the patient's lungs with 100% oxygen. A face mask is adequate for this purpose, but if the anæsthetist can insert an endotracheal tube quickly and easily and without allowing anoxia to develop it is an advantage, because he then has a hand free for assisting in other ways. Meanwhile the surgeon takes a knife, opens the left chest, and at the same time confirms the diagnosis and begins cardiac massage.

Precisely the same course should be followed if the abdomen is already open, but while the surgeon or his assistant is opening the chest there is no reason why the other should not attempt to massage the heart with one hand under the diaphragm and the other over the sternum. Sometimes this will be effective in restarting the heart, as it was in the first successful case which was reported by Starling and Lane (1902). But one must not waste time on these alternative procedures. Cardiac massage is invariably effective in supplying oxygenated blood to the brain, unless there is some obstruction in the circulation between the left ventricle and the cerebral vessels. Percussion of the chest, injection of drugs, and pricking the heart with needles may all be effective on occasions, but they cannot be guaranteed to be effective.

The incision is made in the left 4th, 5th or 6th intercostal space. As it is deepened through the intercostal muscles, one must be careful that the underlying lung is not injured. Once the pleura is opened the lung falls away. The incision must be a long one running from the midline far back into the axilla. If the incision extends far back into the axilla it is certainly possible to make an adequate opening through which one can insert both hands. The ribs must be spread forcibly. If necessary costal cartilages can be divided up and down. The heart is then massaged for a short time through the intact pericardium. It may start. If it does not after 30 seconds or so the pericardium should be opened widely. The heart can then be drawn out and compressed between the two hands. The compression must be between the palms of the hands and not with the tips of the fingers, because if the fingers are used the heart may be perforated. In a child's heart, when it is only possible to use one hand, compression should be between the palm and the thenar eminence and not with the pulp of the thumb, as again this may cause a perforation. The rate of massage should be about 50 per minute. Rates much faster than this cannot be kept up for more than a few minutes because of fatigue. Moreover it is necessary to wait for the heart to fill in diastole before it can be emptied. This is easily appreciated by the two hands round the heart. Electromanometric recordings of the blood pressure from a needle in the brachial artery during cardiac massage have shown pressures of up to 75 mm Hg (Deuchar and Venner, 1953). In another patient when a needle was placed in the aorta a blood pressure of 110 mm Hg was obtained.

If the massage is effective, it should be possible to feel a pulse in a large artery such as the carotid or abdominal aorta. After a short time the pupils, which have become wide and dilated, should diminish in size. If these features are not observed then the efforts at massage must be increased because it is likely that the output is inadequate. Once the blood supply to the brain has been re-established, one can look to restoration of the heart action. The first step is oxygenation of the myocardium and this is done by cardiac massage at the same time as the lungs are being ventilated, so that oxygenated blood is forced down the coronary arteries. The heart, which was pale mauve in colour, will be seen to become pink. Pink areas spread out from the coronary arteries until they gradually coalesce.

Cardiac asystole and ventricular fibrillation must now be differentiated. In asystole the heart is completely motionless and toneless. In ventricular fibrillation there is continuous uncoordinated movement of the muscle fibres. At first this is very feeble, and it may be so feeble that those without experience must look very closely at the heart before being able to observe any movement at all. After massage and other treatment, as the tone of the myocardium improves, the fibrillation becomes more vigorous and coarser until the whole heart is thrown into violent movement by the unco-ordinated contractions. This is a stage in recovery and a stage at which electric defibrillation is likely to be successful. If the heart in asystole does not start with cardiac massage, an injection of either adrenaline or calcium chloride should be used. The injection must be given into the cavities of the heart. It does not matter into which cavity the drug is injected. It is preferable to use large volumes of dilute solutions rather

than a small volume of more concentrated solution, because under these circumstances the needles become detached from the syringes and with a small dose like 1 ml there can be great doubt whether any of it was injected. Therefore one should use 10 ml of 1/10,000 adrenaline or 10 ml of 1% calcium chloride. Another reason for not using 10% calcium chloride is that if it is injected into the myocardium it will produce severe necrosis.

If the problem is ventricular fibrillation the first step is oxygenation of the myocardium by massage. Fibrillation may now change from feeble to coarse. If it does not, an injection of adrenaline will usually produce this effect, and, when the fibrillation is seen to be coarse and the tone of the myocardium is felt to have increased, electric defibrillation can be tried. This is merely a matter of applying a shock of between 1 and 3·8 amps across the ventricular myocardium and for this one needs between 150 and 350 volts. Every operating theatre should now be equipped with a proper defibrillator. The shock must be applied through two large and well-padded electrodes soaked in saline so that good contact is made with the surface of the heart as otherwise it is possible to produce a burn. The shock should be as brief as possible—0·2 to 0·5 of a second. If one shock is not effective serial defibrillation should be used (Wiggers, 1940), giving a series of shocks as quickly as possible one after the other. The whole of the myocardium then becomes asystolic because all the fibres are refractory, and the heart starts again spontaneously or after further massage.

I have obtained much experience in dealing with this problem through cardiac surgery, but it does not require a great deal of experience although it does require some. It is therefore advisable that everybody should practise cardiac massage, both on experimental animals and in the post-mortem room, to become familiar with the technique. The essential feature is speed in initiating treatment. One must acquire almost a conditioned reflex so that there is no need to stop and think. To achieve this is not easy, but it is the only way in which the heavy mortality from this condition can ever be reduced, as it can be, to no more than 10%.

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Dr. J. B. Wyman (London):

Anæsthetic Accidents

If an attempt were made to list all accidents possible during anæsthesia, it would be found that they had already occurred. Who would imagine that a theatre orderly's sense of uniformity was so disturbed that he had to paint all the gas cylinders in the theatre so that they were indistinguishable from those containing oxygen? Or that someone would use an anæsthetic machine delivering cyclopropane and oxygen as an ash-tray, with the consequent disappearance of the said machine? Or that respiratory obstruction could result from such causes as (1) a volvulus of the rebreathing bag, (2) a hiatus hernia within an endotracheal tube, (3) an imperforate endotracheal connector, or (4) a paraphimosis of an endotracheal cuff?

The first principle of anæsthesia is to check the patient, the machine and the drugs. To do this, the anæsthetist must give himself time. He must either, and preferably, arrive some time before the operation, or be prepared to keep his surgeon waiting. The second principle is to watch the patient throughout the anæsthetic both directly and by some form of monitoring apparatus. Whenever possible I use some form of spinal-anæsthetic screen which enables the anæsthetist to watch the patient all the time, and renders it unnecessary for him to burrow under the sterile towels. The form of monitoring varies from simple intermittent blood pressure recordings to complex apparatus. A record of the anæsthetic given and the drugs used should be made. In my own hospital, we keep detailed records of the anæsthetic procedure and events during the operation, and insert a brief summary in the patient's general notes.

Frequently anæsthetists and surgeons, though well acquainted with the cause of some accidents, persist in using suspect techniques. An example is the continued widespread use of 5% thiopentone when it is accepted that the use of 2½% thiopentone will lessen the likelihood of ischæmic damage following the accidental introduction of the solution into an artery. I once deliberately injected without untoward result 10 ml of 2½% thiopentone into the artery of a patient whose limb was about to be amputated for malignant disease, and I strongly urge the general adoption of 2½% thiopentone.

Should this disaster of the introduction of thiopentone into an artery occur, the treatment is, firstly, to get rid of the initial spasm by means of a brachial plexus block or even by sympathectomy. The return of the radial pulse or the relief of spasm and pain does not mean that the danger of gangrene is over for the vessels are already damaged. The second step, therefore, is

the prevention of ischæmic changes by preserving the blood flow through the part until recovery takes place. This is best achieved by keeping the patient on heparin for at least a week and by abandoning the operation, unless absolutely necessary.

The anæsthetist should protect the patient from injuries due to errors in posture. These include post-operative nerve palsies such as those caused by brachial plexus injuries, excessive pressure on thighs and ankles due to prolonged use of unpadded lithotomy poles, and dangling feet and arms giving rise to foot and wrist drop. I advocate the abandonment of both shoulder supports and wrist-harnesses to keep the patient in the Trendelenburg position, and the adoption instead of the corrugated mattress. Though I know it is common practice, I avoid abduction of the arms for intravenous infusions. Traction is the probable cause of brachial plexus injuries and this position can be dangerous. I prefer to have the arms folded across the chest or anchored to the patient's sides by means of plastic hooks.

Explosions.—That some anæsthetic agents are explosive is well known and I am sure that surgeons will always heed the anæsthetists' caution to avoid using the diathermy or cautery on such occasions. The greatest danger to-day, however, is that of static electricity initiating an explosion. While the anæsthetists can insist upon the avoidance of the use of nylon pillowslips and woollen blankets in the theatre, it will take all our combined persuasive power to make our nursing colleagues give up the wearing of dangerous man-made materials while assisting in the theatre.

It is a frightening thought that the anæsthetist who rushes in half dressed for the street and half dressed for the theatre, can, every time he rises from his anæsthetic stool, initiate a spark between the seat of his trousers and the top of the stool in the region of 2,000 to 3,000 volts, and given the right condition of humidity cause an explosion in any anæsthetic gases lurking in the vicinity. The elimination of explosions depends on prophylaxis. Either avoid explosive agents or else take all the precautions recommended.

Vomiting.—The inhalation of gastric contents is responsible for more anæsthetic deaths than any other cause. It is the greatest single cause of maternal mortality during obstetrics. It is a problem to which there is no single and final answer, but the dangers can be diminished. Vomiting is a reflex action. The vomiting centre is situated in the dorsal portion of the lateral reticular formation and receives many afferent impulses, from the higher centres (as in psychic vomiting), the labyrinth (as in motion sickness), the mucosa of the fauces and pharynx (as in induced vomiting), from the stomach and peritoneum, and from the chemoreceptor trigger zone situated on the medullary surface. Various drugs and substances produced in the body reach the chemoreceptor trigger zone via the blood stream and stimulate it to produce vomiting, e.g. opiates, apomorphine, anoxæmia (as in mountain sickness). Similar effects may also result from circulatory changes, such as fall in blood pressure and raised intracranial pressure. Vomiting may be due to a summation of these stimuli. The best example of this is during the induction of anæsthesia for an emergency when there is fear, stimulation of the fauces by anæsthetic gases or premature insertion of the airway, when opiates may have been given and there may be some degree of oxygen lack. Added to all this is the fact that the vomiting centre is most sensitive in the zone between second and third stages of anæsthesia.

The efferent pathway is highly complicated, as is obvious if one considers the mechanism of vomiting. After a deep inspiration, the breath is held, the glottis is closed, the diaphragm is still further depressed with consequent straightening of the œsophagus, and the abdominal muscles compress the flaccid stomach against the diaphragm. From this it is apparent that vomiting cannot occur if the abdominal muscles are paralysed or when the vomiting centre is depressed by deep general anæsthesia (Scurr, 1958, *Broad Way, clin. Suppl.* **3**, cxxx).

Thus, to prevent inhalation of gastric contents during emergency surgery one may, when suitable, use spinal, epidural or local analgesia instead of general anæsthesia. However, if general anæsthesia is essential vomiting may be avoided by the following means: (*a*) Waiting, if possible, until the stomach empties. The stomach is said to empty in about four hours after a meal but this may be delayed by the onset of labour or by trauma. (*b*) Emptying the stomach by induced vomiting. (*c*) Using a technique that gives a smooth induction until the vomiting reflex is depressed by deep general anæsthesia. (*d*) The simultaneous paralysis of respiration and abdominal muscles with loss of consciousness. (*e*) Mechanically preventing gastric contents from entering the trachea or by a combination of these techniques.

Mr. R. H. F. Brain (London):

The Heart Under General Anæsthesia

In most cases both cardiac arrest and ventricular fibrillation develop as a result of myocardial malnutrition from hypoxia, hypercarbia or electrolyte and pH changes. The alternative explanation of excess vagotonia is unlikely since under general anæsthesia gross liberties can be and are taken with the vagus

nerve without ill-effect. Gordon and Jones (1959) suggest that the only difference in ætiology between cardiac asystole and ventricular fibrillation is the degree and duration of malnutrition, asystole following severe acute anoxia, and fibrillation following prolonged but less severe anoxia which leads to the accumulation in the circulation of large quantities of potassium, probably released from the liver as potassium hexosephosphate, though experience of open heart surgery suggests that these two entities are not always easily separable. In general, their explanation is probably correct.

Myocardial malnutrition may occur from inadequate ventilation, hæmorrhage and cardiac manipulation, inadequate ventilation being the most important. From the surgeon's standpoint, prophylaxis consists in prompt and adequate replacement of blood throughout the operation, and the avoidance of any manipulation of the heart that obstructs its circulation such as forcible mechanical retraction, dislocation of the heart from the pericardium, and prolonged obstruction of valve orifices by the finger or instruments. Careful pre-operative appraisal and investigation of the patient is important as it may give forewarning of pulmonary and cardiac conditions predisposing to myocardial nutritional insufficiency during the operation. Hearts with a poor intrinsic blood supply either from coronary disease, aortic valve lesions or right-to-left blood shunts are particularly prone, while the excessive nutritional demands of muscle hypertrophy are difficult to satisfy, particularly hypertrophied left ventricles. For example, when operating on patients with severe calcific aortic stenosis under hypothermia, one may be faced with ventricular fibrillation in which cardiac massage cannot provide a sufficiently effective coronary circulation to enable the left ventricle to be defibrillated, although the right returns readily to a normal rhythm.

Among the pulmonary conditions predisposing to ventilatory insufficiency are bronchial obstruction and increased resistance to ventilation due to fibrous replacement of the pulmonary parenchyma. Emphysematous patients with their voluminous lungs lacking elastic recoil are often extremely difficult to ventilate; inflation even to hyperinflation under pressure is easy but deflation may be almost impossible. Pulmonary massage coincidental with cardiac massage may be necessary to restore a normal heart rhythm under these conditions. The rigid, fibrous, inelastic lung, although less common, poses problems of inflation.

The time of onset of acute heart failure is often remarkably constant, which would appear to correspond to crucial periods in the ventilation of patients both on and off the operating table. A heart rarely gets into trouble during the operation but it seems to remain susceptible for several hours afterwards. Post-operative failure may be subdivided into an early group, typically occurring while the surgeon is dressing or relaxing between operations, and a later group, often in the middle of the subsequent operation on the list. Attendance in the ward at this time reveals a hypotensive, comatose patient, ventilating extremely poorly, with pallor rather than cyanosis, while pCO_2 levels in the blood may be very high. Adequate mechanical ventilation will rapidly restore the blood pressure, full consciousness, and a normal appearance. Failure to recognize this picture in time ends fatally in acute heart failure. It seems relevant at this juncture to plead that surgical shock as an entity should no longer be recognized, tainted as it is with traditional inexplicability and consequent therapeutic immobility.

Finally, it is necessary to stress the premonitory signs of impending cardiac disaster as this leads to a study of the various methods used to monitor the heart during surgery, with a view either to avoiding the disaster of acute failure altogether, or at least to its earlier diagnosis and treatment. Changes in the heart-rate, particularly the onset of bradycardia accompanied by a progressive fall in blood pressure, are of serious significance. Monitoring of the heart-rate and rhythm may be carried out by the electrocardiograph while many cardiac surgeons place great reliance on the EEG measuring cerebral activity and hence indirectly general tissue nutrition. Information on arterial blood gas levels and pH changes would also be a very sensitive guide under most conditions.

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Dr. C. Bishop (London):

Electrical Monitoring of the Cardiovascular System during Anæsthesia

Estimation of the pulse-rate and the blood pressure readily lends itself to routine electrical monitoring during anæsthesia.

The pulse is usually monitored with the electrocardiograph, the undoubted value of which in detecting myocardial damage and pulse arrhythmias hardly needs reiterating here. In recent years, due to advances in electronics, the size of the apparatus has been considerably reduced and the electrical complex can now be observed continuously on a cathode ray tube with a machine sufficiently small to be placed on the anæsthetic trolley. The Videograph is typical of this type of apparatus (Fig. 1). A device which continuously counts and records the pulse rate on a dial has been developed, the so-called

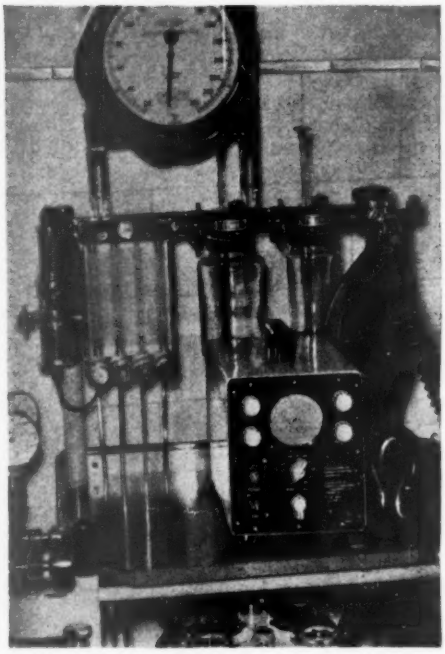


FIG. 1.—The Videograph. A portable electrocardioscope shown in position on a standard Boyle's anæsthetic machine.

cardiotachometer. Used alone this has little practical clinical application, but if incorporated into an electrocardiograph it might be of great value.

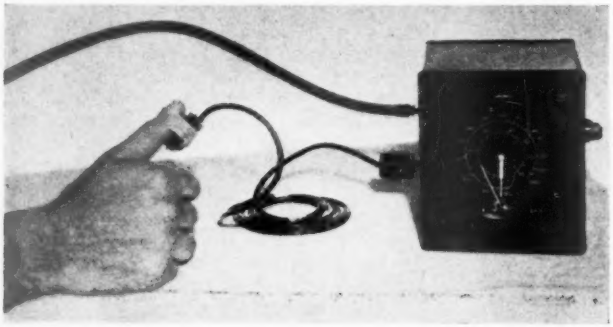
The systemic blood pressure can be measured directly by inserting into a peripheral artery a cannula connected to an electrical manometer. Although this procedure is carried out for total heart-lung by-pass work, it does not lend itself to routine surgical practice. The standard method of estimating the blood pressure indirectly, with an inflatable cuff placed on the upper arm and a brachial stethoscope, has a number of disadvantages in the anæsthetized patient. The elbow is often inaccessible, the stethoscope diaphragm is easily displaced, and, if the tubing is extended or a fall of blood pressure occurs, the Korotkow sounds become muffled or inaudible. A number of devices have been invented in an attempt to eliminate the stethoscope and replace it with some form of electronic pulse detector. The following piece of apparatus has been developed in the Department of Anæsthetics at Guy's Hospital (Bishop, 1958).

Description of Apparatus

It consists, as shown in Fig. 2, of a small carbon microphone which is applied with adhesive strapping to the thumb or big toe. This transmits the pulsations in the pulp bed to an ammeter via an appropriate electrical circuit. The indicator needle of the meter is so arranged that it oscillates over the dial of an aneroid sphygmomanometer in time with the pulse. A blood pressure cuff is placed on the arm or leg proximal to the pulse detector as shown in Fig. 3, and is connected to the aneroid sphygmomanometer. On inflating the cuff above the systolic pressure, the pulse is obliterated and the oscillations cease. The air in the cuff is slowly released until the first oscillations reappear. These correspond to the first Korotkow sounds and the systolic pressure is read from the sphygmomanometer. This is easily seen because the needles of the ammeter and sphygmomanometer are incorporated on the same dial.

Advantages of the Apparatus

The instrument has been used extensively in all surgical departments and has proved invaluable. It is extremely simple to use. The pulse beat is visible throughout the operation, even when a peripheral pulse is not readily palpable, as sometimes occurs in badly shocked patients or in infants. The small size of the child's thumb bed does not affect the ease with which the pulse is detected. It is also of value when a peripheral



←FIG. 2.—The combined pulse indicator and sphygmomanometer, shown with the pulse detector applied to the thumb.

FIG. 3.—The apparatus connected to a cuff applied to the upper arm.

pulse is inaccessible either due to complicated towelling, as occurs in some neurosurgical procedures, or in operations on the severely burnt patient, where the limbs are either involved or are required as donor sites for skin grafts. Irregularities in the pulse-rate from any cause can readily be seen. The time required to estimate the blood pressure is very brief. This allows the infusion rate to be accurately controlled when hypotensive techniques or vasopressor drugs are used. The measurement of the blood pressure is a one-handed procedure, a point of practical importance when respiration is manually controlled. The apparatus uses a low-voltage battery and can therefore be used with complete safety in the presence of explosive anæsthetic agents.

The machine has its limitations for, as the blood pressure falls, peripheral vasoconstriction limits the blood flow through the pulp bed, and the machine fails to detect pulsations below a systolic pressure of about 50 mm Hg.

Monitoring of the pulse and the blood pressure is of supreme importance in the early detection of failure of the cardiovascular system. This is carried out as a routine measure for major cardiac procedures, in which the surgeon has the additional advantage of having the heart under direct vision. How much more important therefore is this monitoring in operations outside the chest, involving procedures which should carry little or no mortality?

Acknowledgments.—I am indebted to Mechanical and Industrial Equipment Ltd., for permission to reproduce the photograph of their Videograph, and to the Editor of *Anæsthesia* for permission to reproduce Figs. 2 and 3.

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BISHOP, C. (1958) *Anæsthesia*, **13**, 329.

Meeting
May 4, 1960

DISCUSSION ON CHOLANGIOGRAPHY

Mr. David H. Patey (London):

Modern surgery of the gall-bladder dates from 1924 when Evarts Graham and Warren Cole developed excretion cholecystography. Only those brought up in surgery before then can appreciate fully the revolution which the introduction of this test initiated. Before cholecystography, surgeons had to rely chiefly on symptoms for the diagnosis of gall-bladder disease, and negative laparotomies were common. In addition, surgeons used to regard such minor and doubtful findings as slight thickening of the gall-bladder wall or an excess of fat around its neck as indicating sufficient gall-bladder pathology to justify cholecystectomy, and felt more than justified if on opening the gall-bladder after removal they found a few flecks of cholesterol in the mucosal folds. But it was not only surgeons who had diagnostic difficulties. Physicians were in the habit of making the diagnosis of chronic catarrhal cholecystitis to explain such symptoms as vague upper abdominal discomfort and a general feeling of ill-health. To-day with the perfection of cholecystography, fat round the neck of the gall-bladder as a sign of cholecystitis and chronic catarrhal cholecystitis have been relegated to the limbo of medical mythology.

But although operations on the gall-bladder, properly performed, are now as completely satisfactory as any in surgery, there has been a growing realization that all is not so well with the surgery of the common duct. Stones in the duct are missed even by experienced surgeons, negative explorations are common, and there is still wide disagreement on the frequency and even the existence of various functional syndromes. The history of biliary surgery since the last war may be summarized as the attempt to bring the same degree of precision into the surgery of the biliary passages as already exists in that of the gall-bladder. Cholangiography occupies such a key position in this attempt that I consider it to be the core of the problem of present-day biliary surgery.

Technique.—Once organic chemists had produced sufficiently bland radiopaque media, cholangiography followed naturally from the practice of surgeons of introducing tubes into the common bile duct after exploration. At first, the custom was to perform the cholangiography some days post-operatively shortly before removal of the tube. But soon surgeons realized that it was better to know during, rather than after, operation if they had left stones in the bile ducts. Hence the practice of operative cholangiography gradually developed. It is on the value of operative cholangiography that there has been most difference of opinion among surgeons, and it is on this that Mr. Le Quesne and Professor Lowdon will concentrate their attention. The main indication for surgery of the biliary passages, as of the gall-bladder, is gall-stones, and Mr. Le Quesne will deal with the value of operative cholangiography in the diagnosis of gall-stones. Professor Lowdon will broaden the discussion by dealing also with cholangiography in the diagnosis of other conditions such as tumours and pancreatitis, and will also touch on the difficult

question of the dyskinesias or functional disorders of the biliary passages.

Operative cholangiography is a combined surgico-radiological and not a purely surgical technique. The close association that we have enjoyed at the Middlesex Hospital with our radiological colleagues, and their routine attendance in the operating theatre for the test, has played an essential part both in developing technique and in interpretation. Dr. Whiteside will speak also on excretion cholangiography. This is at present crude and imperfect, but on a long view it seems destined largely to replace other cholangiographic techniques; and we shall probably have to wait for its perfection before achieving agreement on the postulated dyskinesias. In the meantime, he will tell us what help it may give us, particularly in association with operative cholangiography.

Finally, I will say a few words on the anatomy of the lower end of the common bile duct, for which Mr. Bernard Hand has kindly allowed me to use his not yet published intensive studies. Fig. 1 represents diagrammatically the commonest

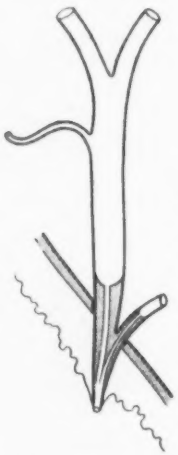

FIG. 1. — Diagram of lower end of normal common bile duct to show terminal narrow thickened segment. For details *see* text. (After Hand, 1958.)

arrangement found. The common bile duct diminishes only slightly in diameter in its supraduodenal course, but a couple of millimetres above the duodenum, and when it is already in the pancreas, the lumen suddenly becomes appreciably narrower. From this point downwards the narrow lumen of the duct continues, slightly diminishing in diameter, to just above the point where the duct joins with the pancreatic duct. This point is thus the narrowest part of the common duct and hence is the point at which calculi most commonly become impacted. The diameter of the common channel formed by the joining of the biliary and pancreatic ducts is in most cases only the sum of the diameters of the two ducts and only in this sense is there an ampulla. Associated with the narrow portion of the duct in its whole length from immediately above the duodenum to its termination, and causing the narrowing, is a thickening of the duct wall resulting partly from a complete ring of circular muscle, partly from connective tissue and glands, and partly from proliferated mucous membrane thrown into folds. The intrinsic muscle of the duct is distinct from that of the duodenum, which surrounds the thickened bile duct in its intramural course, and can obviously also act on the duct. These anatomical points may be helpful in the interpretation of the cholangiograms to be shown by subsequent speakers.

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Mr. L. P. Le Quesne (London):

Operative cholangiography is performed by the injection of radiopaque material into the biliary tree, and may be performed either before (pre-exploratory) or after (post-exploratory) exploration of the common bile duct. The resulting films may give important information concerning the anatomy of the ductal system and the presence of strictures or tumours, but their main value lies in the detection of stones in the biliary passages.

Within the last fifteen years it has become apparent that the clinical and operative criteria for exploration of the common bile duct are inaccurate, resulting on the one hand in the overlooking of stones in the common duct, and on the other in the exploration of many ducts which do not contain calculi. These two results are closely interrelated, since those surgeons with the widest indications for exploring the common duct will have the lowest rate of residual stones but the highest rate of unnecessary explorations. At the Lahey Clinic during the years 1949–52, 1,077 patients underwent operations on the biliary tract (excluding those with stricture of the common bile duct): the common bile duct was explored in 389, but in 65% (251 patients) no stones were found (Colcock and Liddle, 1958). Similar figures could be quoted from many other clinics. This high incidence of fruitless exploration of the duct is not without its cost, for there is evidence from both British (Havard, 1960) and American (Bartlett and Waddell, 1958) sources that the mortality rate following cholecystectomy and exploration of the common duct is higher than that of simple cholecystectomy, whilst the average stay in hospital after operation is longer

(Hight *et al.*, 1959). The recorded incidence of residual stone in the common duct varies widely, ranging from 2% (Colcock and Liddle, 1958) to 20% (Hicken *et al.*, 1954). The reasons for this wide variation are beyond the scope of this paper, but from a survey of the literature the average incidence of residual stone is probably in the region of 5%.

The two types of operative cholangiography have a different contribution to make to the problem of the diagnosis of stone in the bile duct. The object of pre-exploratory cholangiography is to determine whether or not the common bile duct contains calculi and so requires exploration; the object of post-exploratory cholangiography is to confirm that no stones have been overlooked.

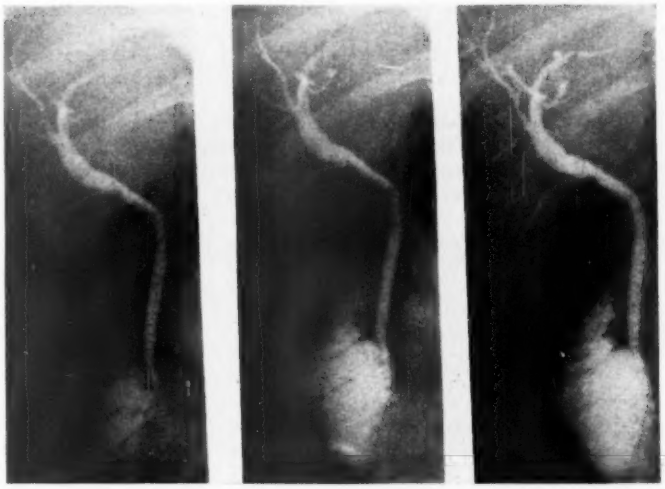

FIG. 1.—The three films from a normal pre-exploratory cholangiogram. The characteristic features are described in the text.

Technique and Interpretation of Pre-exploratory Cholangiogram

The patient is laid on the operating table on a shallow box into which the cassettes can be placed. A fine catheter (a ureteric catheter is suitable) is inserted via the cystic duct into the common bile duct, and three films taken after the slow injection of 3, 6–8, 10–12 ml of 35% Diodrast, the anæsthetist arresting all respiratory movement during each exposure. Certain points of technique are important: (1) To avoid obscuring the films, all instruments should be removed from the operation field and skin towels should be secured by some method other than clips. (2) Before exposing the films the table should be tilted 20 degrees to the right, to throw the image of the common duct clear of that of the spine. (3) Care must be taken to exclude bubbles from the duct system. To this end, before insertion the catheter is filled with saline from a syringe, and after insertion suction is applied before a little saline is injected to test the system. (4) It is essential to expose at least one film after the injection of only a small quantity of dye, to enable the fine terminal portion of the duct to be seen clearly. If films are only exposed after injecting 10 ml or more of Diodrast, the density of dye in the duct and overlying duodenum may well obscure not only this portion of the duct but also small filling defects. With a duct of normal calibre the first film should be exposed after injecting only 3 ml, but if the duct is dilated the amount may be increased to 5 ml, similar increments being made for the second and third exposures.

In examining the films to see whether or not they show evidence of calculi in the duct system attention must be paid to several points other than the presence or absence of filling defects. A normal pre-exploratory cholangiogram (Fig. 1) shows the following features: (1) The duct is of normal calibre, a diameter as measured on the X-ray film of 12 mm being taken as representing the upper limit of normal. (Le Quesne *et al.*, 1959). (2) There is a free flow of dye into the duodenum in all films. (3) The terminal narrow segment of the duct with the characteristic notch at its junction with the wider proximal portion is clearly seen in at least one film. (4) There are no filling defects. (5) There is no excess retrograde filling of the hepatic ducts. Reflux up the pancreatic duct may or may not be seen and does not appear to be related to the presence or absence of stones in the bile duct.

If the films show a deviation from normality in any of the criteria mentioned above the duct must be considered as abnormal and requiring exploration, with one qualification, namely that on some occasions free flow is not seen on the first film. But if the films are in all other respects normal, this can be considered as within the range of normal. In our experience, if these

criteria are rigidly applied it can be confidently concluded that the duct contains no stone. This proof of a normal duct not requiring exploration is the greatest dividend from pre-exploratory cholangiography.

The most obvious evidence of the presence of a stone in the duct is a filling defect, which is often associated with dilatation of the duct and no flow of dye into the duodenum (Fig. 2). In other

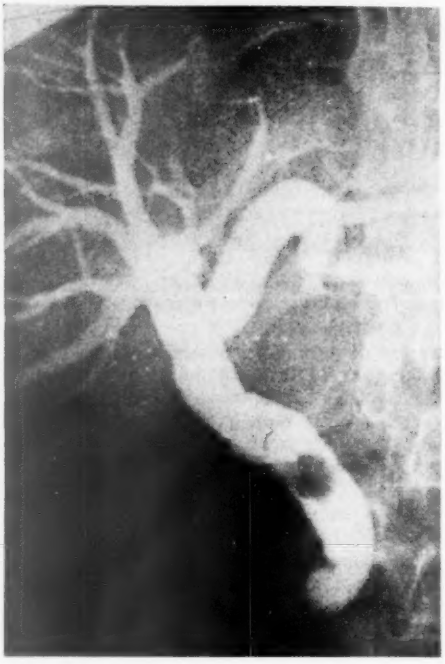

FIG. 2.—Pre-exploratory cholangiogram showing a large filling defect due to a calculus with dilatation of the duct, no flow of dye into the duodenum, and excess retrograde filling.

cases the flow into the duodenum is free, and in some the duct is also of normal calibre. In yet other cases no defects are seen, and the presence of stones is indicated by an interference with flow, usually associated with a failure to visualize the terminal segment of the duct. These two deviations from normal, particularly if associated with dilatation of the duct and excess retrograde filling, are evidence of obstruction to the duct, usually by a calculus, and indicate that exploration of the duct should be performed.

A number of factors can give rise to appearances which may lead to a false interpretation of the cholangiograms. In our experience, if the criteria of normality are rigidly applied, the incidence of false negatives, that is of ducts incorrectly interpreted as being free of stones, is nil. There are, however, two findings which may give rise to a false positive interpretation: air bubbles in the duct, and spasm of the sphincteric muscle surrounding the narrow terminal segment of the duct. Bubbles give rise to filling defects closely resembling calculi, but their true nature is usually indicated because they are spherical and the cholangiogram is in other respects normal. If defects are suspected as being due to bubbles it is our practice to flush the duct freely down the catheter with saline and then repeat the examination, bubbles being removed by this technique while calculi remain. Spasm of the sphincteric muscle impairs the free flow of dye into the duodenum with the result that in some cases the cholangiogram shows a duct of normal calibre, but with no flow into the duodenum and no visualization of the terminal segment, the duct shadow ending in a convex curve. This spasm may be due to irritation of the sphincter by a small stone, but is more usually due to other causes such as the pre-anæsthetic drugs. The true state of affairs can be discovered by repeating the examination after giving the patient amyl nitrite by inhalation, and if no stone is present this will result in relaxation of the spasm with normal cholangiographic appearances.

Value of Pre-exploratory Cholangiography

At the Middlesex Hospital our experience with operative cholangiography can be divided into two periods. From 1953–1957 we were largely concerned with developing the technique and establishing the appearances of a normal duct and the significance of deviations from this normal picture. At the same time Mr. Bernard Hand carried out a study of the anatomy of the lower end of the common duct, correlating his findings with an analysis of the 183 pre-exploratory cholangiograms. As a result of this investigation we were satisfied that pre-exploratory cholangiography, performed with a careful technique and interpreted with scrupulous regard to the criteria of normality, gives reliable evidence on the presence or absence of stones in the duct. Since then we have used this examination as our main guide in deciding whether or not to explore the duct.

From May 1957 to March 1960 we have performed operations on the biliary tract on 121 further patients. In 109 of these a pre-exploratory cholangiogram is available for analysis and the relevant data are set out in Tables I and II. In 74 cases the cholangiogram was considered normal and the common duct was not explored: follow-up of these patients has so far produced no evidence that any of them

TABLE I.—OPERATIONS ON BILIARY TRACT: 121 CASES

A. *Previous Cholecystectomy*	5 Cases	
Residual stone	3	
Cystic duct stump	2	
B. *No Pre-exploratory Cholangiogram*	7 Cases	
Technical failure	3	
Common bile duct explored in 6: stones found in 2		
C. *Leaving for Analysis*	109 Cases	
Stones in gall-bladder	78	
Stones in gall-bladder and common bile duct	19	
Stones in common bile duct only	2	
Cholecystitis glandularis proliferans	7	
Miscellaneous	3	Pancreatitis; Chlorpromazine jaundice; Biliary cirrhosis

TABLE II.—PRE-EXPLORATORY CHOLANGIOGRAM: 109 CASES

Cholecystectomy only	74 Cases	
Cholectystectomy + exploration of common bile duct	34 Cases	
Cholangiogram only	1 Case	
Exploration of common bile duct	34 Cases	
Stones in common bile duct	21	
No stones in common bile duct	13	4 False positive; 9 Other causes*
Unsuspected stone revealed	4 Cases	
Exploration saved	18 Cases	
Bubbles	3 Cases (1 explored)	
Spasm	5 Cases (None explored)	

*Indication for exploration of the duct in these cases was: Pancreatitis 4, dilated common bile duct (? cause) 2, fibrosis of sphincter 1, anatomical reasons 1, infective hepatitis and stones in gall-bladder 1.

harbours a residual stone in the duct. Of the 21 cases where stones were removed from the duct, in 17 the cholangiogram showed a filling defect, usually associated with other radiological abnormalities, whilst in 4 the presence of a stone was only revealed by interference with normal flow or dilatation of the duct. In 13 cases a common duct not containing stones was explored. In 9 of these the decision was dictated by considerations not concerned with the possible presence of a stone in the duct, whilst in the remaining 4 the exploration was undertaken because the cholangiogram suggested the presence of a stone (i.e. false positives). On the other hand, in 4 cases the cholangiogram revealed the presence of otherwise unsuspected duct stones, and in 18 other cases we would have felt obliged from the clinical and operative evidence to explore the duct had we been without the evidence of the cholangiogram.

This analysis illustrates the value of pre-exploratory cholangiography. In a small number of patients it reveals unsuspected stones in the duct, but its greatest value lies in demonstrating a normal duct in patients who would otherwise require exploration of the duct. It is not an unduly long procedure and in many patients shortens their subsequent stay in hospital. For these reasons we believe the examination to be a valuable addition to the surgical management of gall-stones.

Post-exploratory Cholangiography

Post-exploratory cholangiography is performed by injecting Diodrast down the T-tube inserted in the common duct. In general the technique is similar to that of the pre-exploratory examination but two problems make interpretation of the films difficult. Firstly, in many cases, especially if the lower end of the duct has been instrumentally dilated or a sphincterotomy performed, a free flow of dye into the duodenum cannot be demonstrated. In our experience, even in the absence of residual stones, amyl nitrite cannot be relied upon to restore the flow, suggesting that the obstruction is in part at least due to œdema of the lower end of the duct. Accordingly, in this examination a persistent failure to demonstrate the terminal segment and free flow does not indicate that further exploration is required, and the diagnosis of a residual stone must depend mainly on the presence of a filling defect. Herein lies a further difficulty, as even with free irrigation of the duct with saline it is difficult to exclude bubbles. These two difficulties impair the value of the post-exploratory examination.

In the entire series of 121 cases, the common bile duct was explored in 45. In 34 of these a post-exploratory cholangiogram was performed. A residual calculus was revealed in two patients. On 9 occasions the cholangiogram showed no flow into the duodenum and in 3, bubbles gave rise to confusing filling defects. In none of these 12 patients did subsequent post-operative cholangiography show any evidence of residual calculus. Thus, in one-third of the cases either spasm or bubbles gave rise to difficulty in interpretation. While therefore post-exploratory cholangiography may give rise to information of great value, it is not as accurate an investigation as the pre-exploratory cholangiography.

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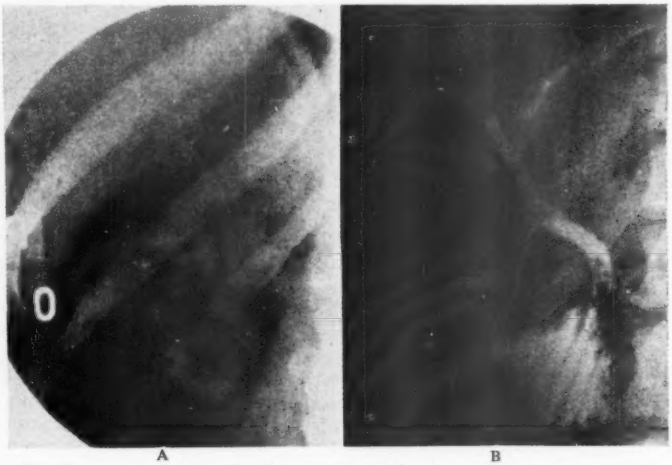
Dr. C. G. Whiteside (London):

In an X-ray Department patients with potential lesions of the bile duct fall into two groups: (1) Those with no history of previous biliary surgery. (2) Those who following cholecystectomy (*a*) have had a recent exploration of the common bile duct, and have a T-tube still *in situ*, or (*b*) present with recurrent biliary symptoms some time after the operation.

We examine patients in the first group initially by oral cholecystography. As a result, we have few patients with cholelithiasis who have had pre-operative intravenous cholangiography, chiefly those with poorly filling gall-bladders or clinical evidence of stones in the duct. Of these, there were 13 who had pre-operative intravenous and operative cholangiograms and from whom stones were removed from the common bile duct. These 13 cases fall into the group analysed by Mr. Le Quesne. All 13 showed an abnormal operative cholangiogram with calculi visible in 10. The intravenous cholangiogram on the other hand was normal in 3 of the 13 cases, doubtful in 4 and abnormal in 6. Calculi were seen definitely in 3 and doubtfully in 4.

The results in this small series indicate that pre-operative intravenous cholangiography is at present inferior to the operative cholangiography in the detection of stones in the duct. On the other hand, there was often a time-interval between the two examinations—between two and seven months in 6 cases—and the 3 normal intravenous cholangiograms all fell in this group. In the other 7 cases the interval was nine days or less and no intravenous cholangiogram was completely normal in this group. During the longer time-intervals some of the stones found in the common duct at operative cholangiography may have reached there from the gall-bladder (Fig. 1).



A B

FIG. 1.—A, a pre-operative intravenous cholangiogram and B, an operative cholangiogram in a case of cholelithiasis; in the interval stones have entered the common duct.

Excretory Oral Cholangiography

The common bile duct may be visualized occasionally on routine oral cholecystography with contrast media such as Telepaque, usually following contraction of a well-filled gall-bladder. Recently, there has become available a new oral medium, Biloptin (sodium ipodate), which is excreted and sufficiently concentrated by the liver like Biligrafin to outline the common bile duct. As a result, the radiologist is no longer completely dependent on the concentrating power of the gall-bladder for success. If the cystic duct is obstructed, no gall-bladder filling will occur but the common bile duct will be outlined and the reason for the absent gall-bladder shadow will be apparent. In our experience, however, detailed examination of the common duct *per se* is more reliable with Biligrafin.

Post-operative T-tube Cholangiography

The purpose of this examination is well known. As a result of the routine use of operative cholangiography for cholelithiasis, post-operative cholangiography has become less frequent. To some extent T-tube cholangiography has been transferred from the X-ray department to the operating theatre to the advantage of both the patient and the surgeon. The examination should not, however, be omitted prior to removal of the T-tube. Spasm of the lower end of the common duct, for example, is common in post-exploratory operative cholangiography and may both preclude a detailed examination of this area in the theatre and render the study of flow of the contrast medium impossible. Both of these defects of operative cholangiography can be rectified by post-operative cholangiography. The examination is performed with a similar technique to that used at operation, i.e. using initially a small quantity of contrast medium to study the anatomy and the flow through the

narrow ampullary segment. Further films to outline the hepatic tree may show residual calculi in the hepatic ducts. Finally the examination records the calibre of the duct for future reference if no operative cholangiogram is available.

Post-operative Intravenous Cholangiography

In the investigation of recurrent symptoms in patients who have had a previous cholecystectomy, intravenous cholangiography finds its most important application. The main purpose of the examination is to exclude any lesion which may be partially obstructing the common duct. If the obstruction is severe, the examination is unlikely to be successful.

Intravenous cholangiography may give information on the calibre of the common duct, the diagnosis of biliary obstruction, and the nature of the obstructing agent.

The calibre of the common duct.—There is considerable disagreement over the variation in diameter of the normal common bile duct. As a result of 47 post-mortem studies of normal biliary tracts, Benson (1940) suggested an upper limit of 6·5 mm which corresponds to a radiographic image of 8 mm. Sullens and Sexton (1955) accept an upper limit of 7 mm, Samuel (1957) of 10 mm, and Wise *et al.* (1957) at the Lahey Clinic of up to 14 mm.

Fig. 2 shows the diameter of the common bile duct measured by Le Quesne, Whiteside, and Hand (1959) radiographically at operation on each of 73 patients undergoing cholecystectomy for stones. Each rectangle represents one case and where stones were removed from the duct, the rectangle is hatched. The lower diagram represents the duct diameter of the same cases measured at least twelve months later on intravenous cholangiograms. 18 cases, or 25% of the total, had stones in the common bile duct and 14 of these had ducts measuring 11 mm or more in diameter. Only 4 cases had ducts of this size not containing a calculus and in two of these four there was highly suggestive clinical evidence (severe pain and jaundice) that a stone had recently been in the duct. Of the 8 cases with duct diameters of 10 mm, only one contained a stone, while of the 55 cases with duct diameters of 10 mm or less, only 4 contained stone.

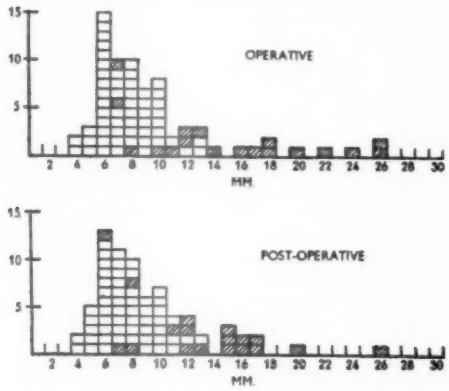


FIG. 2.—*See* text. (Reproduced from Le Quesne *et al.* (1959) by kind permission.)

From these and other considerations, Le Quesne *et al.* (1959) arrived at the following conclusions: (1) The upper limit of the normal diameter of the common bile duct is 10 mm and no duct should be considered dilated unless it measures 12 mm or more radiographically. (2) There is no evidence that the common duct becomes dilated after cholecystectomy. (3) There is no evidence that a dilated common duct diminishes significantly in size after removal of stones from the duct. (4) There is no correlation between the continuance of symptoms after cholecystectomy and the calibre of the common bile duct.

Though stones may be present in ducts of normal calibre (4 out of 55 cases), no stones were found in ducts of 5 mm diameter or less. This agrees closely with a series of 76 patients described by Wise *et al.* (1957) who found no obstruction in ducts measuring 5 mm in diameter or less at operations for post-cholecystectomy symptoms.

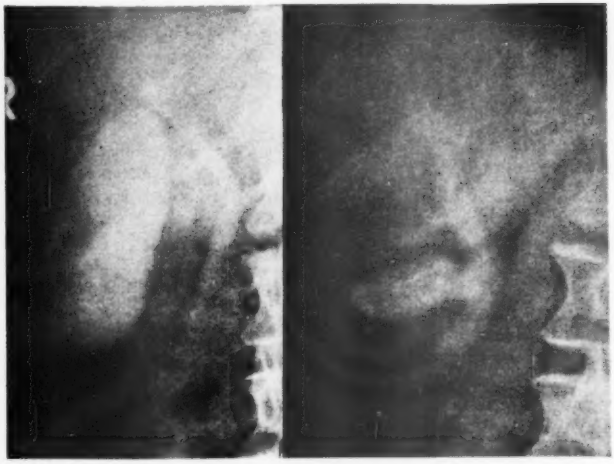
The value of calibre in diagnosis.—The discovery of a dilated common duct must be interpreted quite differently in pre-operative and post-operative cases. In the former, a dilated duct nearly always implies existing obstruction to the duct (14 out of 18 cases in this series); in the latter, it is of no significance in itself in the absence of radiographic records of the size of the duct at operation. As a natural corollary, if it can be shown from such records that the duct has increased in size, this is a finding of the greatest importance and signifies some obstruction of the duct. Conversely, if it can be shown that post-cholecystectomy symptoms are not associated with any increase in the calibre of the duct, then the duct is unlikely to be obstructed.

Where no records of previous calibre exist, the problem is more difficult. While ducts measuring 5 mm or less are unlikely to be obstructed, others may be partially obstructed and dilated and yet fall within the normal range of measurement; on the other hand large ducts may not necessarily be obstructed. Thus, in the problem of differentiating obstructed from unobstructed ducts, an isolated observation on calibre is of limited value.

The diagnosis of biliary obstruction.—Wise *et al.* (1957) describe three cardinal signs in biliary obstruction: (1) The biliary radicles in the liver are distended. (2) The duct loses its normal tapered shape and becomes tubular with obstructive dilatation. (3) The density of the contrast medium in the duct does not fall off after one hour, as it normally does, but persists up to two hours after injection. The use of morphia to close the ampulla and so improve visualization of the duct is therefore contra-indicated.

The following case illustrates some of these features:

A patient was admitted with acute pancreatitis. Nine months later she had cholecystectomy for gall-stones. No stones were found in the common duct at operation and post-operative cholangiography was normal. The pancreas was indurated. She was well for two years and then began to have recurrent attacks of pain radiating to the back. The films (Fig. 3) showed that the common duct was normal prior to operation. The cholangiogram two years later showed some increase in the diameter of the duct, a loss of normal tapering of the lower end, and persistence of density of contrast medium in the duct at two hours. The duct diameter was still within normal limits but the loss of tapering indicated dilatation.



A B

FIG. 3.—Intravenous cholangiograms. A, Pre-operative, showing normal duct which B, demonstrates obstructive signs two years post-operatively. Relapsing pancreatitis.

It would seem that where the obstructing agent is not radiologically or clinically obvious, the retention concept may be valuable and a film two hours after injection should be a routine procedure. Our experience in this field is very limited and we can offer no comment, except to note that in their series of partial obstruction, retention was present in less than 50% of cases.

The nature of the obstructing agent.—The radiological appearances of calculi are well known and require no further elaboration. When small they are often difficult to detect and good radiographic technique is consequently of the greatest importance. Calculi which are freely mobile in the duct add to these difficulties. The secondary signs of partial obstruction described above and particularly the study of changes of calibre of the duct are valuable in such cases where the cause of the obstruction is not visible. This applies also to pancreatitis and fibrosis of the ampulla. Extrinsic pressure from adhesions may occasionally cause partial obstruction. Finally it is worth noting that the presence or absence of visible contrast medium in the duodenum is of no value in determining partial obstruction of the common bile duct (Wise and O'Brien, 1956).

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Professor A. G. R. Lowdon (Newcastle upon Tyne): After an early phase of great expectations, we have found intravenous and oral cholangiography of limited value. The significance of a dilated duct is not always clear: it may suggest present or previous obstruction by stone, but sometimes dilatation is the result of other diseases—chronic pancreatitis, fibrosis of the sphincter of Oddi or dyskinesia. However, a dilated duct in the pre-operative cholangiogram in a patient who has had a previous cholecystectomy and whose present symptoms are apparently of biliary origin may rightly be taken to be an encouragement to re-operation. My radiological colleagues have had some success in demonstrating radio-lucent stones in the duct system by using tomography with intravenous cholangiography, and it appears that this technique may be helpful when the object of the investigation is the detection of stones.

Operative cholangiography has been practised now for so many years that it is surprising to find

that the surgical profession, at least in this country and in America, still seems undecided or divided about its value. It is not used as a routine except by a small number of surgeons in this country. This may mean that it is not worth doing. On the other hand if we think it is worth doing, we must be prompted to ask why the measure is so unpopular. The answer, doubtless, is that the technique is, or appears to be, time consuming, and that until the drill has been practised to perfection many frustrating mistakes occur. Bad pictures mean repeating the whole process or accepting that time and effort has been wasted. There is also the inevitable movement and disturbance in the theatre when the X-ray machine must be wheeled into position and the cassettes changed, unless the surgeon is fortunate enough to have a permanent built-in X-ray unit.

All these difficulties can be overcome by careful planning and some training of the team. Mr. Le Quesne has described the technique in some detail. We use a long cassette tunnel which lies on the operating table and the cassette is inserted from the head end on an implement like a baker's shovel. This was copied from arrangements I saw in the Middlesex Hospital and I think it is better than lifting the towels at the side of the patient for each cassette change. A better picture is obtained if a grid is employed over the cassette. I have used a small metal cannula for insertion into the duct; this is connected by a long piece of narrow-gauge plastic tubing to the syringe. The plastic tubing has the advantage that it is transparent and air bubbles in the fluid can be seen and thus avoided. To insert a metal cannula into the common bile duct through the cystic duct, the cystic duct often has to be gently dilated, by inserting and separating the points of fine forceps.

Mr. Le Quesne has dealt mainly with the use of operative cholangiography in patients with stones in the common bile duct and I shall refer to this subject only briefly, though I agree that it is the common and the most important indication. I think some of the disrepute of cholangiography in the diagnosis of duct stones stems from the thoughtful paper by Johnston, Waugh and Good (1954, *Ann. Surg.*, **139**, 293) in which they claimed that their surgical techniques had proved to be more reliable than cholangiography in detecting common duct stones. "The method", they wrote, "must become more accurate before it can replace surgical exploration of the ducts by experienced surgeons, or become a routine part of choledocholithotomy". This is essentially, I imagine, the case of those who still think that operative cholangiography is not worth while, or, to be frank, not worth the trouble.

In the first place, it must be contended that the method has indeed become more accurate, as has been shown by the contributions to this Discussion. This reliability does seem to justify us in trusting a *good* negative cholangiogram obtained at the operation and deciding on these grounds not to perform choledochotomy even with a previous history of jaundice or some dilatation of the duct.

In the second place, apart from using cholangiography to avoid unnecessary exploration of the duct it has its important uses as a supplement to, rather than a substitute for, careful surgery. I have found it invaluable as a post-exploratory measure to make sure that all stones have been removed from the duct. Most, if not all, surgeons have come to accept that a post-operative cholangiogram should be made through a T-tube before it is removed. Surely it is only a reasonable extension of thought to conclude that this examination should also be made before the abdomen is closed.

I have on more than one occasion avoided the mistake of leaving stones behind by the help of operative cholangiography. In one patient after residual stones had been shown in this way the duct was re-explored and four more stones removed. Another cholangiogram showed that there were still two stones in the dilated duct. I then performed a transduodenal sphincterotomy and sphincteroplasty, which is I believe much the best way to deal with the problem of inaccessible stones left in the hepatic ducts or indeed any case of recurrent duct stones. The point illustrated by a case like the one I have described is that X-rays at the time of operation can be a factor contributing to the perfection of technique and the improvement of results. Supraduodenal choledochotomy as a means of getting all the stones in a duct system is proved to be a fallible technique and anything that will make it less fallible should be welcomed.

If cholangiography is to be used routinely in the course of operations on the biliary tract, the surgeon must be prepared to meet and interpret other abnormalities in the X-ray picture. Among the less common abnormalities which can be recognized are: low junction of cystic and common duct; dilated duct associated with chronic pancreatitis in which the portion of the duct passing through the pancreas shows an irregular narrowing; obstruction of the duct by carcinoma of the head of the pancreas when the block may be at the level of the upper border of the pancreas; high obstructions of the duct system by tumour arising in the hepatic duct; obstruction at the lower end of the common duct resulting from carcinoma of the ampulla of Vater; reflux of dye into the pancreatic duct which may be normal or sometimes excessive if

there is fibrosis or spasm of the ampullary sphincter.

But not all dilated ducts are obstructed. One patient had biliary symptoms for twenty years; these persisted without relief after cholecystectomy. At re-operation the head of the pancreas was firm and nodular but there was no jaundice. Cholangiogram showed massive dilatation of the ducts but in spite of this the dye flowed quickly and easily into the duodenum. The pressure readings in the common duct were low. The patient was treated by right splanchnicectomy and has been very well for five years since then.

At this point of course we have entered the very controversial field of biliary dyskinesia and this is not the subject under discussion, but I have felt obliged to refer to it because I myself believe that dyskinesia is a real entity and that we will not understand all the findings of cholangiography except eventually with the help of manometric studies of the biliary tract. I have relieved several patients with severe post-cholecystectomy biliary pain by performing transduodenal sphincteroplasty, and I have seen others who were apparently suffering from the same kind of dysfunction of the sphincter dramatically relieved by vagal section on the lesser curve of the stomach. I am not prepared to go on record as saying that these neurectomies are the right or the only way to deal with the problem of dyskinesia, but I think it is relevant to our subject to this extent that the more careful study of the ducts by cholangiography must lead us to further study also of their functional behaviour and misbehaviour.

Mr. H. A. Kidd (London):

Percutaneous transhepatic cholangiography consists of putting a needle through the skin and the liver into a bile duct, aspirating the bile and then injecting diodone 45%. Antero-posterior and lateral X-rays are then taken. I have used this method since 1952 in cases of jaundice which are not suitable for investigation by other methods, including Biligrafin (Kidd, 1956*a*, *b*). Experience with this technique has shown that if the bile duct is not entered after three attempts then it is not dilated and the jaundice is not obstructive in origin, so an unnecessary laparotomy may be avoided. When jaundice is present this method is used: (1) To investigate the cause of biliary symptoms after cholecystectomy. (2) To diagnose the presence and site of a carcinoma affecting the biliary system. (3) To demonstrate the presence, location and number of calculi in the bile ducts. (4) To measure the pressure of bile in the biliary system. (5) To diagnose the presence of obstructive jaundice as opposed to non-obstructive jaundice.

Technique.—A point is chosen in the abdominal wall just below the costal margin at the junction of the outer and middle third of a line going from the mid-line to the flank. The skin is infiltrated with procaine and a special needle, 20 mm in length and 1 mm in diameter, is introduced at an angle of 65 degrees to the horizontal and 15 degrees to the vertical. As the needle is passed through the liver frequent aspirations are made with a small syringe and saline is used to clear the needle should it become blocked. Blood is often aspirated from small vessels but when one of the hepatic ducts is entered white bile is withdrawn. The pressure may be measured and samples taken for bacteriological and chemical analysis. In order to get good films great care must be taken to empty the biliary system of bile completely and to refill it with diodone; this will often require 40 c.c or more of the dye. Antero-posterior and lateral films are taken and then repeated after further aspiration and injection of dye.

Difficulties and dangers.—In a series of over 40 cases there has been no mortality from this procedure, nor has there been any trouble from bleeding from the liver or from accidental perforation of the colon or small bowel. The chief danger is accidental puncture of the gall-bladder and if this happens bile will be aspirated after the needle has been inserted for only a short distance. As much bile as possible should be aspirated and 5 c.c of diodone injected. Films are then taken to show the point of the needle and the condition of the gall-bladder. The needle can then be pushed further in until a bile duct is entered and cholangiograms taken by the previously mentioned technique. As there is a greatly increased biliary pressure in these cases a laparotomy should be performed and the gall-bladder removed as leakage of bile causing biliary peritonitis can occur. The gall-bladder was punctured in 2 cases in this series: in one there was no biliary leak as the gall-bladder had been entered after the needle had penetrated some liver substance; in the other pain occurred in the evening after the examination and a cholecystectomy and removal of biliary calculi was performed followed by an uninterrupted recovery.

An apparatus was demonstrated which is used as a guide to introduce the needle at the predetermined correct angles and can also be used for making corrections should there be difficulty in finding a dilated duct.

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Section of Endocrinology

President—Professor F. T. G. PRUNTY, M.D., F.R.C.P.

Meeting
April 27, 1960

The Management of the Adrenogenital Syndrome

By DOUGLAS HUBBLE, M.D., F.R.C.P.
Birmingham

THERE is only a partial block in the synthesis of hydrocortisone in the adrenogenital syndrome. The amount of hydrocortisone formed, however, is always inadequate to suppress corticotrophin formation by the anterior pituitary although the androgenizing substances may not be formed in sufficient quantity to cause abnormally advanced height increments and skeletal maturation, and in the two girls in our series who remained untreated for periods of one year and five years there was no increase in the relative size of the phallus. The amount of hydrocortisone formed by the adrenal cortex, while yet insufficient for the suppression of corticotrophin, is adequate for the maintenance of health. Even in stressful situations these children do not run into trouble except when they are salt losers. The adrenal cortex not only makes hydrocortisone in adequate amounts but is also capable of further response to corticotrophin stimulation. However, no matter how mild the adrenogenital syndrome and how negligible the advancement of height and skeletal maturation, adrenocortical hyperplasia will continue inexorably and ultimate height will be retarded unless treatment is instituted.

The following are four unusual clinical presentations of the adrenogenital syndrome.

A.—The Virilized Child of Average Length and Bone Age with Mild Adrenocortical Hyperplasia

Case I.—H. B. This girl has congenital virilizing hyperplasia and was observed without treatment until she was 1 year old. Her height age and bone age (Fig. 1) kept on the 50 percentile despite the steady advancement in her urinary steroid output—the 17-ketosteroids increasing from 1·5 mg/24 hours at three months to 4·2 mg/24 hours at 1 year, and the 17-hydroxycorticosteroids (17-OHCS) from 2·4 to 8·8 mg/24 hours. The pregnanetriol output at two months was 0·9 mg/24 hours (average of 4 estimations) and at 1 year was 1·1 mg/24 hours.

B.—Boys in Whom the Adrenogenital Syndrome has Continued Untreated

Although the advance of height is rapid, the acceleration of skeletal maturation is faster so that these children never achieve their predictable height.

Case II.—J. L. In this patient in whom the adrenogenital syndrome was not diagnosed until he was 6 years old, there is no doubt that corticotrophin suppressive therapy must be undertaken. His height age is 8½ years but his bone age is 12–14 years. The total output of adrenocortical steroids as judged by their urinary metabolites—17-KS 12 mg/24 hours, 17-OHCS 40 mg/24 hours (average of 3 estimations)—is about eight times that of the average for his age.

Case III.—R. T. This boy is now 15 years old, his epiphyses have fused and his growth is complete at 5 ft. 1 in. The diagnosis of the adrenogenital syndrome had been made correctly at the age of 7 years before the days of cortisone therapy and he had escaped from medical supervision until he was 14.

Wilkins (1959) says that the "only reason for continuing cortisone therapy is to bring about testicular maturation and fertility, the desirability of which is open to question . . . after puberty cortisone therapy can be discontinued and virilization allowed to proceed unchecked". However, there are theoretical reasons for suppressing adrenocortical hyperplasia and for checking the production of abnormal corticosteroids. All patients with this syndrome should be treated whether pre-puberal or post-puberal, and whether

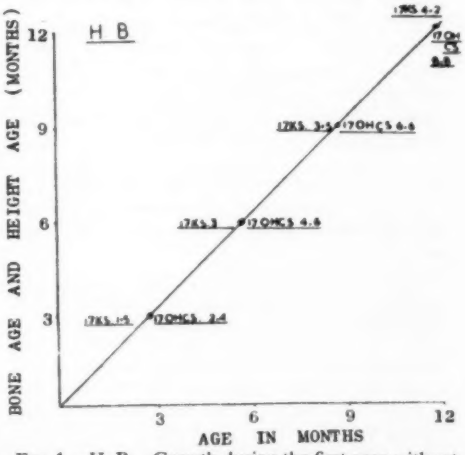

FIG. 1.—H. B. Growth during the first year without treatment.

or not the epiphyses have fused. Even in boys in whom growth has ceased, treatment of the adrenogenital syndrome should be undertaken.

C.—Patients with the Adrenogenital Syndrome in Whom Sexual Maturation is Occurring or has Occurred Without Treatment

There is variation in the production of the anterior-pituitary sex hormones in the adrenogenital syndrome. These are usually but by no means always suppressed by the excess of androgens and œstrogens secreted by the adrenal cortex.

In Case II the testes are much larger than is normal for a boy of his age. Since his gonadotrophin output is only 5 mg HMG /24 hours it is possible that the increased size of his testes is related to excessive androgen stimulation, but there can be no doubt about the activity of the anterior pituitary sex hormones in Case IV.

Case IV.—M. N. This girl, now aged 15 years, developed normally until the menarche at 10 years. With the onset of menses there was increasing hirsuties which was her presenting complaint. The daily urinary excretion of 17-ketosteroids was 33 mg, of 17-OHCS 49 mg, of pregnanetriol 5 mg, and of gonadotrophins 30 mg HMG (Brooks *et al.*, 1960). And yet menstruation had been entirely regular for the intervening five years. Bone fusion was complete and her height 5 ft. 2 in.

Here again there was no need for suppressive therapy unless it is agreed that uncontrolled adrenocortical hyperplasia and the circulation of large quantities of abnormal steroids are in themselves undesirable. Certainly the condition of adult women in whom this process has been allowed to proceed unchecked with consequent male baldness and amenorrhœa is not desirable. Even in patients with normal sexual function, treatment of the adrenogenital syndrome should be undertaken. The genetic question of whether these homozygotes should be allowed to reproduce requires consideration, but I feel that they should. For those who are salt-losers the question of reproduction is more difficult.

D.—The Girl who has been Reared as a Boy

A serious problem is management of the girl with the adrenogenital syndrome who has been reared as a boy.

Case V.—P. F. at the age of 6 years was diagnosed as a male pseudo-hermaphrodite with hypospadias because of a misinterpretation of the nuclear sex chromatin, which was later shown to be chromatin positive. Despite this error "he" had been treated with cortisone, and was referred again with enlargement of the breasts and a monthly discharge of blood from the phallus.

Faulty diagnosis is less likely in the future but there is still considerable difficulty in the diagnosis in boys in whom there may be no obvious abnormality of the genitalia at birth and in infancy. Girls, whose true sex has not been established till later childhood, present a difficult problem in management. It has been shown (Money, 1958) that it is usually unwise to change the sex of rearing—the sex of environment—for this is the most powerful influence in determining the sexual orientation of the individual in his early years. It is thought unwise to change the "boys'" sex after the age of 3 years. I have had 3 patients with this problem. One, a "boy" then 8 years old, was allowed, with the consent of his parents, to revert to his constitutional sex. This was done three years ago and the girl, as she now is, appears to be without psychological trauma. However, this required a considerable amount of staff work and his parents decided before the necessary operations were done that they would leave the district in which they were living.

In the other 2 cases, one of whom is Case V, it was decided in consultation with the parents that the sex of rearing should not be changed and a complete pelvic clearance was done, leaving the small phallus. This situation must always create considerable difficulty of decision. If the sex of rearing is changed there is danger of profound psychological trauma, but if the boy continues in the sex of rearing then normal sex life and, of course, reproductive life are impossible. In girls who have been reared as boys the sex should not be changed after the age of 4–5 years, unless special circumstances exist.

Management of the Adrenogenital Syndrome

At the Birmingham Children's Hospital we found diagnosis much facilitated in infants by the use of the new method recently described by Morris (1959) and applied to diagnosis in the adrenogenital syndrome by Hill (1960). The great advantage of this method is that it can be performed on a single specimen of urine. The urinary 17-ketogenic steroids with no oxygen function at C 11 (ætiocholanolone) (Fraction 2) are fractionated from the 11-oxygenated 17-hydroxycorticosteroids (Fraction 3). The ratio of Fraction 2 to Fraction 3 in the urine of normal children is less than 0·5; in the adrenogenital syndrome it is greater than 1.

The principles of management of these children are well known. Steroid dosage must be continuously assessed. Growth charts must be accurately kept and carefully studied. Failure to make average height increments means that too much steroid is being given, and transfer of the height record from a channel to the one above suggests that the dosage is inadequate. The elective time for surgery in virilized girls is from

2–4 years of age. Most surgeons prefer complete extirpation of the clitoris, which has been shown not to interfere with feminine libido, and it is necessary to disclose fully and adequately the vaginal orifice.

The maintenance dose of steroids should be increased by two and a half times in moderate stress and by five times in severe stress, such as surgical operations. Patients who are salt-losers will require intravenous saline when surgery is undertaken. Severe reactions have been observed during most childhood infections (Rosenthal *et al.*, 1960).

During the last year we have treated our patients with dexamethasone, which has proved quite satisfactory. It is possible to adjust the dose to avoid a "Cushingoid" reaction, the only side-effect we have encountered. The main value in using small-dose steroids is that their urinary metabolites can be disregarded when assaying the output of urinary steroids. A non-salt-retaining steroid is preferable in suppressive therapy, and a salt-retaining steroid such as 9-alpha-fluoro-hydrocortisone given in addition to salt-losers. The 7 patients in whom we have used dexamethasone have been well controlled by a daily dose of 1 mg or less, varying with age.

Fig. 2 (Case II) shows that an adequate suppressive effect is achieved in a few days, but that the maintenance dose has to be assessed carefully. A dose of dexamethasone 0·1 mg×3 daily was inadequate in this boy, but he has been controlled by 0·25 mg×2 daily.

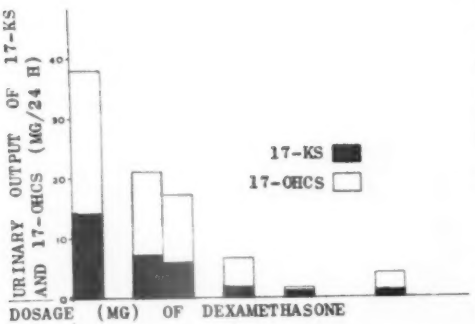

FIG. 2.—J. L., male, aged 6. Adrenogenital syndrome. Urinary output of 17-ketosteroid and 17-hydroxycorticosteroid on dexamethasone therapy, showing the suppressive effect of dexamethasone on steroid output.

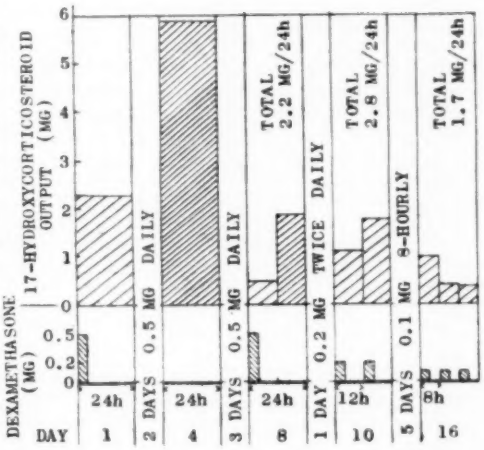

FIG. 3.—C. J., aged 9 months. Showing inadequate suppressive effect of dexamethasone when given in a single daily dose.

Fig. 3 shows some findings in a baby who was a salt-loser. If the dexamethasone was given in a single morning dose (0·5 mg) the urine in the first twelve hours of the day contained <0·5 mg 17-OHCS, while in the second twelve hours it contained 2 mg 17-OHCS, indicating a rapid release from corticotrophin suppression. If, however, the drug was given in smaller and divided doses, 0·1 mg three times a day, the eight-hour specimens showed a reasonably uniform excretion, and the total steroid output in the twenty-four hours was 1·7 mg as against 2·2 mg/24 hours on the larger dose of 0·5 mg. This boy requires 0·1 mg 9-alpha-fluoro-hydrocortisone daily in addition.

In some children adequate suppression is maintained by giving a single daily dose. Two sisters, aged 9 and 4 years, were controlled throughout the twenty-four hours by giving one dose of dexamethasone (0·5 mg and 0·25 mg respectively) in in the morning.

The salt-losing syndrome fully engages the diagnostic and therapeutic resource of the pædiatrician. The emergency state is frequently prolonged and the clinical course of the disease is stormy throughout the first few months of life. We use 9-alpha-fluoro-hydrocortisone in doses of 0·1 mg daily or 0·1 mg twice daily, in addition to dexamethasone or some other non-salt-retaining steroid. Salt should still be added to the diet, even when the need for a salt-retaining drug has passed. If hypertension occurs during therapy it is usually not due to 9-alpha-fluoro-hydrocorti-

sone, but to the other steroid used for corticotrophin suppression.

Acknowledgments.—I am grateful to Dr. A. C. Crooke in whose Department the gonadotrophin assays were made; to the consultant pædiatricians, the family doctors and the school medical officers who referred these cases to me, and to Mr. B. Atkins who performed the urinary steroid estimations.

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Adrenocortical Tumour, Hypoglycæmia and Excessive Secretion of Compound S

By ROGER WILLIAMS, M.B., M.R.C.P.

(*London*)

HYPOGLYCÆMIA has been occasionally reported in adrenal tumours. The following is an account of 2 cases in which hypoglycæmia was the main clinical feature, associated with an unusual pattern of steroid excretion.

Case I.—A female clerk of 24 was admitted to the Middlesex Hospital in 1955 with a four-month history of ankle swelling, acne and increased growth of hair. On examination she was mildly virilized, blood pressure was 220/130 mm Hg and there was a large mass in the left upper quadrant. Following admission she complained of headache and diplopia, before breakfast and on one occasion after fasting became drowsy and sweated profusely. These symptoms were promptly relieved by oral glucose.

Investigations showed a hypokalæmic alkalosis and a high 17-hydroxycorticoid and ketosteroid excretion (Table I). *At operation* a large adrenal tumour weighing over 2 kg was removed. Following this the blood pressure fell, hypoglycæmic symptoms disappeared and the levels of steroid metabolites in the urine returned to normal.

TABLE I.—URINARY STEROIDS IN CASE I

	Before operation	After operation
Total 17-hydroxycorticoids	162 mg/24 h	7·2 mg/24 h
Pregnanediol	10·0 mg/24 h	
Pregnanetriol	0·9 mg/24 h	
Cortisol (9·5–81·5)	367 µg/24 h	
Corticosterone (2·2– 9·0)	33·6 µg/24 h	
Aldosterone (4·6–18·9)	5·8 µg/24 h	
17–ketosteroids	56·8 mg/24 h	0·9 mg/24 h
Dehydroisoandrosterone	19·9 mg/24 h	0·2 mg/24 h

Normal range in brackets.

She remained well for nearly nine months and then developed secondary spread and with this a return of hypoglycæmia. *On admission* she was deeply comatose and despite large doses of intravenous glucose continued to have frequent hypoglycæmic attacks with blood sugars ranging from 40 to 45 mg%. Urinary steroid estimation showed a high 17-ketogenic fraction (174 mg/24 hours), tetrahydro-S constituting 70% of the total. As there appeared to be some response to ACTH pituitary stalk section was carried out but she died shortly afterwards. At post-mortem there were massive secondaries in the liver, the total mass weighing 9·4 kg. The pancreas was normal and an extract of tumour tissue showed normal insulin-like activity.

Case II.—A 48-year-old labourer was admitted to the Hammersmith Hospital in January 1959 with a two-month history of increasing breathlessness on exertion, paroxysmal nocturnal dyspnœa and ankle swelling. He was in gross congestive cardiac failure with a blood pressure of 220/140 mm Hg, and was also noted to be sweating profusely and to have a rather red face. He responded well to routine treatment and was discharged but in May was readmitted complaining of abdominal discomfort and attacks of trembling associated with a feeling of weakness.

On examination the facial flushing and sweating were much more marked, extended to all the exposed areas, and were more or less persistent though aggravated by emotion and possibly by fasting. He had a hard irregular liver extending almost to the pelvis and diffuse weakness and wasting in the upper limbs and proximally in the lower limbs. Blood pressure, however, was well controlled at 150/100 mm Hg, and the venous pressure was normal.

Investigations showed hypoglycæmia with a fasting blood sugar of 37 mg%. The oral glucose tolerance test is shown in Fig. 1 and also the response to sub-

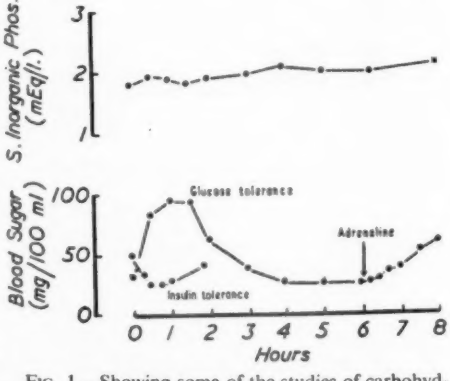

FIG. 1.—Showing some of the studies of carbohydrate metabolism in Case II. Doses used: Glucose 50 g by mouth, insulin 7 units i.v., adrenaline 1·5 ml of 1 in 1,000 soln. s.c.

cutaneous adrenaline. There was no significant change in the serum inorganic phosphate level during this test. The insulin sensitivity, done at a later date, is also shown. Serum insulin-like activity was normal (Dr. P. Wright). Liver biopsy consisted entirely of neoplastic tissue, the histological appearances being those of an adrenocortical tumour.

The cells contained large amounts of glycogen and a second biopsy taken directly into carbon dioxide snow showed absence of glucose-6-phosphatase activity (Dr. A. G. E. Pearse). The total 17-hydroxycorticoid excretion was over 400 mg/24 hour, tetrahydro-S forming 70% of the glucuronide fraction (210 mg) and 47% of the sulphate fraction (115 mg). Pregnanediol and pregnanetriol were also present in excess.

He went rapidly downhill and at post-mortem there was a large adrenal carcinoma with massive secondaries in the liver. Of interest was a section of thigh muscle which showed marked necrosis of the fibres.

The Common Clinical Features and Disturbance of Steroid Biosynthesis

These 2 cases showed many points of similarity. In both the main clinical feature was hypoglycæmia. Both had hypertension and both showed a similar pattern of steroid metabolites in the urine. This was characterized by the presence of large quantities of tetrahydro-S which presumably was derived from excess secretion by the tumour of compound S (17-hydroxy, 11-deoxycorticosterone). Compound S is believed to be one of the naturally occurring precursors of cortisol and in normal subjects only small quantities can be detected in the adrenal vein blood. The finding of large quantities of the tetrahydro derivative, which is its main metabolite, in the urine of these patients probably indicates a block in 11 β-hydroxylation. A similar pattern has been observed in occasional cases of congenital adrenal hyperplasia (Eberlein and Bongiovanni, 1955) and rarely in adrenal carcinoma (Rosselet *et al.*, 1954; Touchstone *et al.*, 1957). Possibly it occurs more commonly than is at present realized for compound-S appears to be physiologically inert and consequently these tumours can easily be regarded as non-functioning unless steroid assays are performed.

Eberlein and Bongiovanni (1955) regard hypertension as one of the characteristic features of congenital adrenal hyperplasia in which there is a deficiency in 11-hydroxylation. They attribute this to excess secretion of deoxycorticosterone though hypertension has not been recorded in all the cases with this defect in steroid biosynthesis (Gandy and Keutmann, 1958). In the present cases the hypertension certainly appeared to be related to the adrenal tumour for in both it was of recent onset and in the first the blood pressure dropped to normal on removal of the tumour. Unfortunately deoxycorticosterone was not looked for in this patient but in the second case it was found to be within normal limits.

The reason for the extreme facial flush in the second case is not known though most probably it was related to adrenal hyperfunction. The marked proximal weakness and muscle necrosis is also unexplained, the possibilities being that either it was a form of steroid myopathy or that it was due in some way to the disturbance of carbohydrate metabolism.

The Mechanism of Hypoglycæmia

There have been previous reports of hypoglycæmia occurring in association with adrenal tumour (Anderson, 1930; Lawrence, 1937; Broster and Patterson, 1948; Staffieri *et al.*, 1949) and hypoglycæmic symptoms, sometimes induced by stress, have been described in occasional cases of congenital adrenal hyperplasia with adrenal virilism (White and Sutton, 1951; Wilkins *et al.*, 1952; Conn and Seltzer, 1955). In the latter it has been attributed to defective cortisol synthesis resulting from the block in 21- or 11-hydroxylation. Yet it has been shown that these blocks are usually relative and in our first patient there was clinical and biochemical evidence of increased cortisol production. In the second patient the excretion of cortisol metabolites was in the lower part of the normal range. In the cases described by Touchstone *et al.* (1957) although the excretion of tetrahydro-S accounted for 45–92% of the α ketolic metabolites the output of cortisol and its metabolites was usually increased, though it is of interest that one of his patients also had hypoglycæmia.

This leads to the broader problem of why hypoglycæmia occurs occasionally in other non-pancreatic tumours such as retroperitoneal fibrosarcomas and primary hepatomas. It has been suggested that these tumours secrete an insulin-like-substance (August and Hiatt, 1958) but in the present cases the insulin-like activity both of serum and tumour tissue was within normal limits. Another possibility is that it is due to hepatic insufficiency but again this cannot be the explanation here for the liver function tests were normal during life and in the first case hypoglycæmia occurred at a time when there were no macroscopic liver secondaries. It seems more likely that hypoglycæmia is related in some way to excess glucose utilization by the tumour. The intense glycolytic activity of neoplastic tissue is well known (Hiatt, 1957) and the common feature in all the reported cases and also in the present ones has been the massive size of the tumours. McFadzean and Yeung (1956) found that in primary hepatomas, as in our second case, there was little change in the serum inorganic

phosphate level during the glucose tolerance test, and concluded that glucose was being diverted away from the periphery. They also found a poor or no response to subcutaneous adrenaline despite significant quantities of glycogen in the tumour. The probable explanation is that the neoplastic tissue lacks glucose-6-phosphatase as was indeed demonstrated in our second patient.

In conclusion we believe that the hypoglycæmia in the present cases was of the same nature as that occurring in other non-pancreatic tumours and was not related to the abnormal steroid metabolism.

Acknowledgments.—I should like to thank the numerous people who have studied various aspects of these cases particularly Dr. T. Chalmers who looked after the first patient, Dr. P. Hugh-Jones, Dr. J. D. N. Nabarro, Dr. J. D. H. Slater and Drs. A. E. Kellie, A. P. Wade and E. R. Smith who performed more of the steroid assays.

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The following paper was also read:

Studies on Endemic Cretins in the Belgian Congo.—Professor P. A. BASTENIE, Dr. A. ERMANS, Dr. O. THYS, Professor M. DE VISSCHER and Dr. C. BECKERS (Brussels, Belgium).

Meeting
May 25, 1960

Stein-Leventhal Syndrome.—D. R. LONDON, B.M., M.R.C.P. (for F. T. G. PRUNTY, M.D., F.R.C.P.)

Mrs. V. S., aged 21, was referred as a possible case of Cushing's syndrome from another hospital where her 17-ketosteroids were estimated at 24·8 mg/24 hours and 17-ketogenic steroids 32·1 mg/24 hours. Her periods appeared when she was 13 and were normal until the age of 17, when she became pregnant. After a daughter had been born by Cæsarean section, the patient's periods became very scanty and irregular. Her weight, following the pregnancy, increased from 10 st. to 15 st. She had been hirsute since puberty.

On examination she was obese, had red striæ on her breasts, gross hirsuties of the face, limbs and abdomen, a male distribution of pubic hair, and acne on her face and back. There were no other physical abnormalities.

The blood picture and electrolytes were normal. The glucose tolerance test showed delayed absorption. The resting 17-ketosteroids were 12·3, 21·9 and 17·2 mg/24 hours rising, after stimulation with ACTH 20 units b.d. for four days, to 33 mg/24 hours. The control 17-ketogenic steroids were 11·1, 8·1 and 10·7 mg/24 hours, rising to 48 mg/24 hours after ACTH. Cortisol production was 31 mg/24 hours, based on urine tetrahydrocortisol and tetrahydrocortisone. Urine free cortisol was 20 μg/24 hours. Androgen production was 17·5 mg/24 hours based on urinary androsterone after intravenous injection of ^{14}C-androstenedione. On this day, the 17-ketosteroids were 17·2 mg. Twenty-four-hour excretion of gonadotrophins, estimated by mouse uterine weight, was 32·5 HMG/20A units per day. Radiography following pneumoperitoneum showed two grossly enlarged ovaries (Fig. 1), a finding confirmed at operation (Mr. G. W. Garland). Histology of the tissue removed at wedge resection demonstrated follicular and lutein cysts with marked mitotic activity in both granulosa cell and thecal layers (Fig. 2). There was more than one primordial ovum in the epithelial layers of some of the follicles.

The original diagnosis of Cushing's syndrome was excluded by the normal 17-ketosteroids and 17-ketogenic steroids, the normal urine free cortisol, and the cortisol production, which, although high, is below the level found in overt Cushing's syndrome (Brooks, 1960). The diagnosis of Stein-Leventhal syndrome was confirmed by the findings on radiology, at operation and by the histology of the operation specimen. The past history of a pregnancy was no bar to the diagnosis (Stein, 1958).

The only unusual feature was the solitary high gonadotrophin (Stein, 1959). This cannot be ascribed to ovulation as the patient was having a period at the time of the urine collection. The method used for this determination does not allow a distinction to be made between F.S.H.

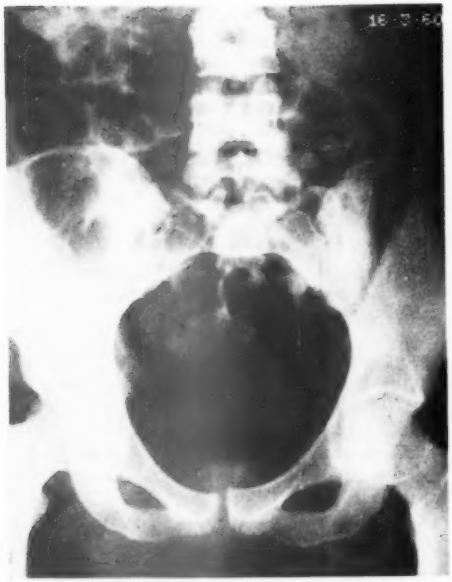

FIG. 1.—Radiograph showing bilateral enlargement of the ovaries.

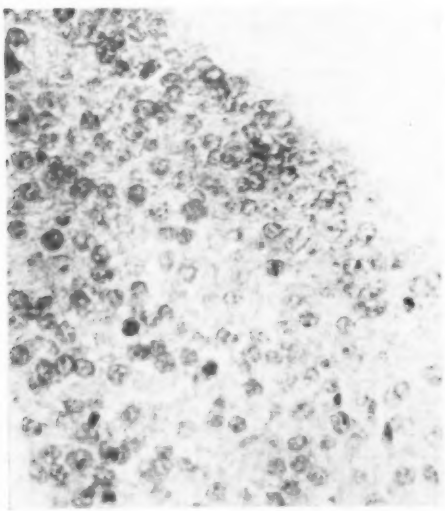

FIG. 2.—Lining of an ovarian follicle. The multiple mitotic figures are visible. ×230.

and L.H. Evidence has been offered that patients with the Stein-Leventhal syndrome produce excessive amounts of L.H. (Keettel *et al.*, 1957), but there are no data available to suggest an oversecretion of F.S.H. in this disorder.

That this patient was producing excessive androgens is suggested by the gross hirsuties and acne. Furthermore the androgen production is considered to be high, although confirmatory evidence on this point is limited. The excess androgen may be coming from either the ovary or from the adrenal. That the ovary is capable of producing androgen is well documented (Savard *et al.*, 1957; O'Donnell and McCaig, 1959; Mills *et al.*, 1959). Androstenedione and 17-hydroxy progesterone, but no œstrogen, were found in the follicular fluid of a case of Stein-Leventhal syndrome from our department (Short, 1960).

However, it is unlikely that in this case the ovary was the sole source of androgen, for the ketosteroid response to ACTH was normal. Thus it is probable that, in this patient, both the ovary and the adrenal were the sites of the excess androgen production.

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Stiff-man Syndrome with Atypical Hypopituitarism.—J. D. H. SLATER, M.B., M.R.C.P.

P. H., male, aged 64.

Progressive, persistent, painful stiffening of pelvic girdle and thigh muscles developed slowly during the autumn of 1957. By February 1958 he was unable to walk, the knees and hips being fixed in flexion. No other muscle groups involved. No generalized tetanic spasms but very painful localized spasms occurred on palpation of the affected muscles and also spontaneously on attempted movement.

On examination (June 1958).—Drawn and ill-looking with loss of skin elasticity and subcutaneous fat. Legs held flexed at about 90 degrees at hips and knees by persistent contraction of the flexor and extensor muscles of both joints. Coarse fasciculation of muscles present. Muscle stiffness only slightly diminished by Pentothal anæsthesia. Arm and ankle deep tendon reflexes present but sluggish. No myotonia. Plantar responses flexor. No sensory abnormalities. Visual fields normal. Body hair, body pigment and testicles probably normal for his age. Blood pressure 85/55–120/90 mm Hg. Jugular venous pressure normal. Generalized scaly skin rash (first appeared in 1956).

Investigations

Muscle. — Electromyography (Dr. A. T. Richardson): The affected muscles showed normal spontaneous motor unit activity in some areas with regions of electrical silence alongside. Lower motor neurons, peripheral sensory neurons and muscle fibres appeared intact.

Microscopy showed some variation in size of the muscle fibres with condensation and "lining up" of sarcolemmal nuclei. These changes were minimal and were present in both normal and stiff muscles. No change occurred following treatment.

Electrolyte composition (Professor J. N. Cumings): Both affected and unaffected muscles had normal content of Na, Mg and Cl on a dried weight basis. K content of stiff muscle normal (415 mEq/kg).

Sodium metabolism and body "space" measurements.—Persistent hyponatræmia (mean 122 mEq/l.) and hypochloræmia (mean 85 mEq/l.) were found with normal levels of serum K (4·0 mEq/l.), bicarbonate (26 mEq/l.) and blood urea (17–19 mg/100 ml). Plasma osmolarity 250 m.Osm/l. Total exchangeable Na was in the high normal range (53 mEq/kg), suggesting that the hyponatræmia was due to dilution and not to deficiency of sodium. Total exchangeable K normal (37 mEq/Kg). Total body water normal (33·5 l. with phenazone and 34·5 l. with urea; mean=64% of body weight) but the apparent extracellular fluid volume was greatly expanded (21·0 l. with ^{82}Br, 20·6 l. with inulin and 19·0 l. with NaCNS). Plasma volume also raised (74·2 ml/kg).

Rapid intravenous infusion of 431 mEq Na as 5% NaCl resulted in slight transient improvement of muscle pain and stiffness.

Renal function.—Glomerular filtration rate (inulin) 107 ml/min. Effective renal plasma flow (PAH) 544 ml/min; filtration fraction 0·197. Urine specific gravity ranged from 1001–1018. Calculated urine osmolarity exceeded 600 m.Osm/l. on occasion. Normal response to salt loading and salt restriction.

Hæmatology. — An apparent anæmia was present. Hæmoglobin 61% (9·0 g/100 ml), hæmatocrit 30%, M.C.H.C. 29%, M.C.V. 89 c.mm. Red cell fragility reduced. Plasma Fe 32μg/100 ml; vitamin-B_{12} absorption normal.

Radiology.—Skull, chest, spine, pelvis, knees and hips normal except for mild osteoarthritic changes. Pituitary fossa normal. Barium meal normal.

Calcium.—Serum Ca 9·3 mg/100 ml, phosphate 3·0 mg/100 ml and alkaline phosphatase 6·6 K.A. units/100 ml. Urine calcium output (on normal ward diet) 220 mg/24 hours.

Glucose tolerance.—Normal. No fall in plasma phosphate or serum K. No glycosuria.

Endocrine glands.—Adrenals: Excretion of water load (20 ml/kg body weight) markedly impaired (15% and 19% in four hours) but corrected by 100 mg oral cortisone (65% and 94% in four hours). Urine total 17-OH corticosteroids, and 17-ketosteroids in normal or low normal range (17-OHCS 5·2–11·6 mg/24 hours; 17-KS 4·5–11·2 mg/24 hours). Plasma Porter-Silber chromogen normal (free 8, conjugated 6 μg/100 ml) (Dr. D. N. Baron). Brisk response to corticotrophin.

Thyroid: ^{131}I neck uptake at twenty-four hours diminished (8%, 9% and 16% of dose) and 0–48 hour urine ^{131}I excretion elevated (74%, 75% and

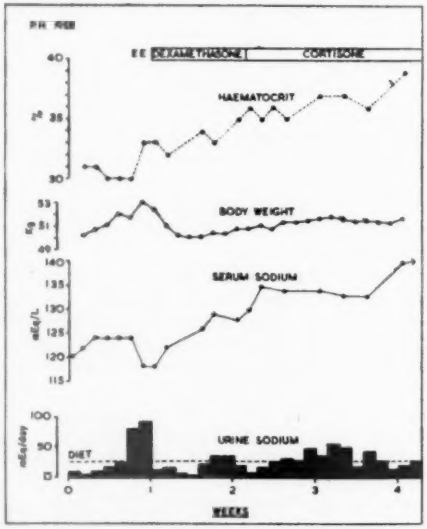

FIG. 1.—Rise of serum sodium concentration and hæmatocrit without significant change of body weight or sodium balance when treated with dexamethasone (0·5 mg b.d.) and then cortisone (12·5 mg t.d.s.).

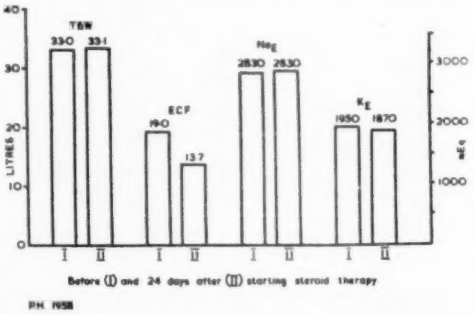

FIG. 2.—Total body water—TBW (phenazone space), extracellular fluid volume—ECF (thiocyanate space) and total exchangeable sodium—Na_E—and potassium—K_E—before and after steroid therapy.

72% of dose). B.M.R.+3%. After T.S.H. ^{131}I neck uptake rose to 47% of the dose in 24 hours.

Pituitary: Urine follicle stimulating hormone output less than 4 mouse-units per twenty-four hours. No rise of urine 17-OHCS output when given an 11-β-hydroxylase inhibitor (SU 4885), suggesting limitation of corticotrophin reserve.

Electrocardiography showed low voltage complexes with flat T-waves which became normal after treatment.

Progress.—Because there was some evidence of impaired pituitary function he was given dexamethasone in physiological doses (0·5 mg b.d.). Within seven days, most of his muscle stiffness had disappeared. The serum sodium concentration and hæmatocrit became normal. The extracellular fluid volume fell considerably within four weeks without measurable change of total body water, body weight, sodium balance and total exchangeable sodium or potassium (Figs. 1 and 2).

Since December 1958 he has been taking prednisone 2·5 mg t.d.s. and L-thyroxine 0·1 mg t.d.s. and has remained symptom free except for some slight residual flexion deformity due to fibrosis around the hip and knee joints.

Comments.—The clinical picture of slowly progressive painful muscle stiffness without any other demonstrable clinical abnormality was described by Moersch and Woltman (1956) under the heading "stiff-man syndrome". Our patient closely resembles many of theirs, but differs from the two patients reported by Asher (1958) and Price and Allott (1958) in that he never developed generalized tetanic convulsions (although painful localized spasms were very troublesome), there were no periods of remission and his mental state has always been normal.

Impairment of anterior pituitary function was not suspected clinically but was suggested by the metabolic studies undertaken to elucidate the nature of the persistent hyponatræmia. However, the fact that a water load could only be excreted normally in the presence of steroids, the low ^{131}I neck uptake (repeated ×3) which was corrected by T.S.H., the low follicle-stimulating hormone output and the restoration of the electrocardiogram to normal following treatment all provide reasonably convincing evidence of partial hypopituitarism.

Tendon contractures of the lower limbs without demonstrable abnormality of the muscles has been described in 5 patients with Addison's disease treated with deoxycortone (DOCA) (Thorn, 1951; Aubertin and Bergouignan, 1951; Adams *et al.*, 1953). The condition is relieved by the administration of cortisone or adrenocortical extract. Recently Wisenbaugh and Heller (1960) have described a patient with classical Addison's disease who developed flexion contractures before any treatment had been given. In all these cases there was undoubtedly a profound disturbance of sodium and potassium metabolism. In our patient, however, the only metabolic abnormality found was in water distribution within the body which implied considerable diminution in the intracellular fluid volume.

A similar abnormality of water distribution is also seen in other conditions, particularly severe malnutrition (Medical Research Council, 1951) and infusion of hypertonic saline did not exacerbate the muscle stiffness in our patient. Therefore cell-shrinkage *per se* is unlikely to be the cause of the muscle spasm. The evidence strongly suggests, however, that our patient's muscle stiffness and partial hypopituitarism are causally related. The mechanism remains obscure.

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Acromegaly Treated by Needle-Implantation of ^{198}Au seeds into the Pituitary Gland, showing changes in growth, carbohydrate and calcium metabolism. — M. T. HARRISON, M.D., M.R.C.P., G. F. JOPLIN, M.R.C.P., M. HARTOG, M.R.C.P., and RUSSELL FRASER, M.D., F.R.C.P.

S. R., male, aged 39.

History.—Acromegaly diagnosed elsewhere in 1956, and first treated early in 1959 with external irradiation 3,500 rad. This caused no regression of acromegalic appearance, nor of the headache; mild diabetes mellitus then developed. Patient first seen at Hammersmith Hospital, July 1959.

On examination (July 1959).—Gross acromegalic appearance; tongue, hands and feet conspicuously enlarged. Thyroid impalpable. Clinically euthyroid. No visual defect.

Investigations (*see* Table I) confirmed activity of acromegaly. Lateral skull film showed a greatly enlarged pituitary fossa of 210 sq mm (normal <130 sq mm), with undercutting of the anterior clinoids and thinning of the dorsum sellæ.

TABLE I.—SUMMARY OF INVESTIGATIONS

	Pre-implant (Oct. 1959)	Three months Post-implant (Jan. 1960)
Hand volumes (right/left : ml) ..	653/605	550/500
Insulin tolerance test: (11·1 units S.I./sq.m). Sum of blood sugars at 60, 90 and 120 min. (n<135)	189 Abnormally = Resistant	68 Abnormally = Sensitive
Prednisone load test: change in overnight urinary sugar after 20 mg at noon, 4 p.m., 8 p.m. (n<50 mg/h)	29——→366	27——→39
Urinary calcium (mg/24 h) on 550 mg/day intake (n<200)	300	160
Sr. test for exchangeable calcium (n=8–18 plasma units) ..	17·3	18·9
Daily deposition of calcium (n=1·0–2·0 plasma units) ..	2·4	1·9
Plasma citrate (mg%) (n=1·5–3·0)	5·50	2·15
UR. 17-KS mg/24 h	8, 13, 18, 22	3, 2, 4, 6
UR. 17-KGS mg/24 h	5, 9, 6, 7	1, 1, 1, 0
Cortisol production rate (Dr. C. Cope, ^{14}C cortisol test) in mg/24 h (n=6–20)	(not done)	2·5
^{131}I *test:* 48-hour neck uptake % (and T) .. (n=25–50); [T(n=3–13)]	55 (6)	37 (3·7)
Water diuresis test (1 litre) % diuresis in 4 hours	59, 43, 52	14
Growth hormone assay (serum) .. .. (n=80–240 μg/l)	461	at 3/12 261 at 6/12 295

Treatment (13.10.59).—*Transethmoid implantation* of two seeds of ^{198}Au into pituitary tumour. (13·3 mc each.) Dosimetry calculations from the post-implant X-rays showed that 45% of the gland received >20,000 rads (60%>10,000 rads), and that the peak dose to the diaphragma sellæ (assuming normal position) was 8,000 rads. For a short period after the implant there were signs of pituitary infection which subsided with antibiotics. A small maintenance dose of cortisone became necessary.

Clinically the acromegalic features clearly regressed by six weeks, and headache ceased altogether.

Test evidence of improvement (Table I).—(1) *Soft tissue changes:* Measurement of hand volume by displacement of water (Falta, 1915) showed a significant decrease of 16% after therapy, the error of the method being not greater than 5%.

(2) *Carbohydrate metabolism:* (*a*) In order to detect abnormal resistance to insulin, as occurs in acromegaly or Cushing's syndrome, we have found it of value to carry out an insulin tolerance test using a larger dose of insulin than in the conventional test. After 11·1 units/sq.m, the rate of return of blood sugar levels to normal is observed (Fig. 1). In normal subjects the sum of the blood sugar levels at 60, 90 and 120 min. after injection

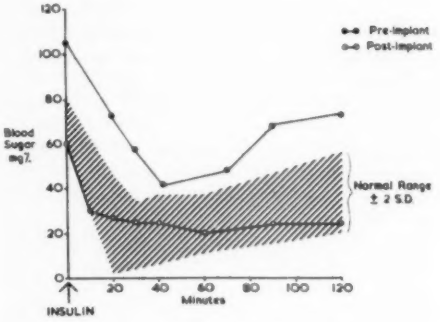

FIG. 1.—Insulin tolerance tests.

of this dose of insulin is less than 135 mg%. Thus he was clearly resistant before treatment, and became sensitive after. (*b*) Prednisone test: Measurement of the overnight urinary excretion of glucose following 3 doses of prednisone four-hourly permits separation of prediabetic from normal subjects (Joplin *et al.*, 1960). Glycosuria is normally slight, not exceeding 50 mg/hour. Table I shows the responses of our patient before and after treatment, and indicates that this diabetic tendency has disappeared.

(3) *Calcium metabolism:* Fig. 2 shows the

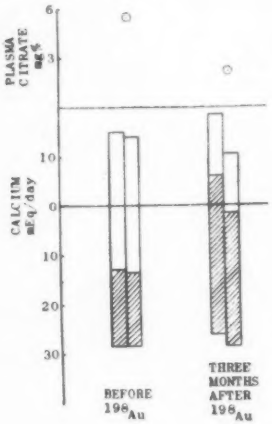

FIG. 2.

calcium balances before and after treatment. initially there was an excessive calcium loss in the urine, together with a low fæcal output. Both these features disappeared after treatment, although the net balance remained about the same. It is of interest that his plasma citrate levels were initially high (Fig. 2) and fell to normal.

A negative calcium balance in acromegaly has been recognized for some years (Bauer and Aub, 1941) and may be the cause of the osteoporosis which sometimes develops. The cause of this and of the hypercalciuria is unknown, but the finding here of a high plasma citrate level is probably relevant. This change may be related to increased parathyroid function, since the parathyroid glands are enlarged and often adenomatous in acromegaly (Cushing and Davidoff, 1929) and we have shown that growth hormone has a parathyrotrophic action in rats (Fraser and Harrison, 1960). The increased rate of bone formation in our patient, shown by the strontium tracer test (Fraser *et al.*, 1960) is also suggestive of hyperparathyroidism.

(4) *Growth hormone assay:* Levels of growth hormone in the serum were assayed by an immunological technique with tanned red cells. The level was abnormally high before therapy and fell significantly afterwards.

These newer tests appear to be of value both in the diagnosis of acromegaly, and in the assessment of effects of therapy.

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Hashimoto's Disease with Complement-fixing Antibodies to Several Human Organs.—DEBORAH DONIACH, M.D. (for R. VAUGHAN HUDSON, F.R.C.S.).

J. L., male, aged 64. The patient, a dental surgeon, was in good health and quite unaware of having a goitre, which was first noted in February 1959 when he attended hospital for laryngitis and smoker's cough. The thyroid was found to be very firm, diffusely enlarged to an estimated 60 g with no thrill or bruit, quite painless and larger on the right so that carcinoma of the thyroid was suspected. The patient was euthyroid, looked young for his age and had normal skin and hair. He denied feeling cold or tired and had no choking sensation. Bowels regular, pulse 72 regular, blood pressure 140/80. No eye signs and no evidence of pretibial myxœdema. Liver and spleen not palpable, no œdema. No albuminuria or glycosuria.

Past illnesses.—Always healthy except for fairly frequent attacks of tonsillitis and laryngitis, and chronic cough (25–30 cigarettes daily). Typhus fever in 1914 war, left inguinal herniorrhaphy in 1948 and again in 1956. Infected parotid duct 1954. No thyroid swelling had been noted on 3 previous admissions to the Middlesex Hospital. However, on the first admission in 1948 the trachea was noted to be central while in 1956 it showed "slight deviation to the right" and the ESR was 21 mm in one hour (Wintrobe, normal 0–15) which suggests that the thyroid condition may have developed between these two dates. His weight was 10 st 8 lb on the first admission and has not changed in the last twelve years. No history could be elicited of any episode suggestive of past hyperthyroidism and there was no history of past jaundice, rheumatic fever or any allergic manifestations or skin rashes.

Family history.—Patient's sister has had thyrotoxicosis with fairly severe exophthalmos and ocular pareses for some years, treated with antithyroid drugs and radioiodine since 1956, and subsequently required permanent thyroid replacement. Mother, father and 6 other siblings had no thyroid disease.

Investigations.—B.M.R. = +15% (Robertson-Reid standard, normal −15 to +15), serum cholesterol 240 mg%, ^{131}I uptake 29%/24 hours, urinary excretion 48%/24 hours. Forty eight-hour plasma radioactivity 0·7% with protein-bound fraction of 0·6%/litre. Scintigram showed a uniform thyroid-shaped uptake pattern with higher counts over the larger right lobe. Triiodothyronine (T_3) given in doses of 120μg daily for eight days (Werner's test) suppressed the thyroid uptake to 2%/24 hours and the total forty eight-hour plasma level to 0·04%/litre. Seroflocculation tests gave normal results with thymol turbidity of 3 units, zinc sulphate turbidity 10 units, colloidal gold 1 unit. However, electrophoretic strip showed raised gamma globulins, and serum protein estimation gave a reversed A/G ratio: total proteins 6·9, A 3·7, G 3·2 g%. Serum bilirubin 0·6 mg%, alkaline phosphatase 9·5 K.-A. units. Immunological tests: tanned cell hæmagglutination test positive to a titre of 250,000, thyroglobulin precipitin in agar gel positive up to 1/8 serum dilution (weak), complement-fixation test (C.F.T.) with whole thyrotoxic thyroid homogenate positive to 1/128 serum dilutions. C.F.T. also positive with other human organs including liver, kidney and suprarenal. In view of this, further studies were undertaken using subcellular fractions of human liver and thyroid obtained by differential centrifugation in a Spinco ultracentrifuge (Roitt *et al.*, 1960) with the following results:

Cell fraction used as antigen	*C.F.T. titre (patient's serum)*
Liver nuclear fraction	64
Liver mitochondria	<512
Liver "microsomes"	256
Liver souble antigens (supernatent fraction)	16
Thyrctoxic thyroid "microsomes"	16

The L–E cell test proved negative but Coons' fluorescent antibody method showed staining of the nuclei in a thyroid section suggesting the presence of antinuclear factors in the patient's serum. The patient's serum also proved cytotoxic to thyroid cells in tissue culture (*see* Pulvertaft *et al.*, 1959).

Follow-up.—On administration of L-thyroxine 0·3 mg daily the goitre gradually decreased in size to an estimated weight of 35 g in 1 year, and became softer. The patient felt no different and continued in perfect health so that in February 1960 he decided to try doing without tablets and stopped taking thyroxine of his own accord. He felt no worse and slept rather better, his smoker's cough troubled him less. In May 1960, the goitre was again very firm, tense and about 80–100 g in size, still not producing pressure symptoms, while the patient remained euthyroid and full of energy. Antibody tests repeated at intervals during the sixteen months' follow-up showed persistently high tanned cell titres with positive precipitin reactions, while the C.F.T. titres fluctuated somewhat. The patient was advised to resume thyroxine therapy in order to reduce the size of his goitre and to avoid any risk of malignant transformation which might be encouraged by the continuous TSH overstimulation and lymphoid hyperplasia obviously going on in his thyroid gland.

Comment.—Hashimoto's disease is rare in men and a recent survey of 303 cases investigated immunologically in our laboratory showed a sex ratio of 12 F/1 M, which agrees with figures published from other parts of the world (Woolner *et al.*, 1959). The finding of thyrotoxicosis in a close relative is not uncommon and suggests that an abnormality of the thyroid might have preceded the auto-immunizing thyroiditis in the patient. No evidence of underlying thyrotoxicosis could be demonstrated in our case on present investigation as shown by the complete suppression of ^{131}I uptake obtained with T_3. Overt hyperthyroidism does not appear to have existed at any time in this man but one cannot exclude an abnormality which, although clinically silent, might have provided the continuous immunological stimulus necessary for progressive auto-sensitization. We have not yet had an opportunity of testing the patient's sister for auto-antibodies but the fact that she became hypothyroid soon after ^{131}I therapy suggests that she may also have some thyroiditis.

As a rule auto-antibodies are strictly organ-specific to the thyroid gland in Hashimoto's disease but about 10% of patients give positive complement-fixation reactions with other human organs (Roitt and Doniach, 1958) particularly liver and kidney, and this does not appear to be necessarily associated with any clinical disturbance in these organs. This phenomenon was studied in hospital patients with various diseases by Mackay and Gajdusek (1958) and other workers (Hackett *et al.*, 1960). It is not yet known to what extent these non-specific reactions can be considered as true auto-antibodies although they certainly occur much more frequently in patients suffering from systemic lupus erythematosus (S.L.E.), in whom a general disturbance of immunological tolerance appears to exist. From a practical point of view it is important to control positive thyroid CFT reactions obtained in goitre patients with tests done concurrently using human liver as an antigen to avoid mistakes in diagnosis due to non-organ-specific reactions. In the present patient only a fraction of the C.F.T. titre could be attributed to specific thyroid "microsome" antibodies.

Hashimoto's disease and primary myxœdema sometimes occur in association with S.L.E. or with allied conditions such as lupoid hepatitis and rheumatoid arthritis. In these cases the patients have high titre thyroid antibodies as well as L.E. cells and/or positive Waaler-Rose tests. A small number of patients with uncomplicated Hashimoto's disease also have antinuclear factors in their serum but hardly ever in amounts sufficient to produce a positive L.E. cell test. In these cases the antinuclear reaction can only be demonstrated by the sensitive fluorescent antibody technique (White, 1959) and it is unlikely that the patients will ever develop clinical manifestations of S.L.E. The theoretical implications of these relationships between thyroid auto-immunity and more widespread diseases of the immune mechanisms are at present under study (Hijmans *et al.*, 1960).

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(*Meeting to be continued*)

Clinical Section

President—T. C. HUNT, D.M.

Meeting
March 11, 1960

Argentaffinoma of Ileum with Carcinoid Syndrome. —W. F. W. SOUTHWOOD, F.R.C.S., and J. E. LENNARD-JONES,[1] M.B., M.R.C.P. (for A. G. PARKS, M.Ch., F.R.C.S.)

Man, aged 60. Admitted for hæmorrhoidectomy, when a large nodular liver was found on routine examination. Laparotomy revealed a small carcinoid tumour of the ileum with hepatic metastases. After operation the significance of the patient's high facial colour was appreciated for the first time; it would not otherwise have aroused comment.

History.—For over twenty years this patient has experienced flushing, usually after meals or on first rising; recently it has been so severe that his workmates commented on it in the canteen after lunch. Over the last eight or ten years his complexion has changed to a mottled red, and during the last two years he has noticed for the first time numerous small spots (angiomata) on his face, trunk and arms. He has not been troubled by diarrhœa, embarrassing borborygmi or breathlessness on exertion, nor lost weight.

On examination.—The plethoric complexion was due to numerous capillary angiomata on his forehead and cheeks. Angiomata, resembling "spider nævi" but without a central arteriole, were also scattered over the trunk and arms, but not the legs. A pink flushing of the face after meals was observed; this flush could be induced by alcohol or by close questioning on ward rounds and affected the face only. The liver was irregular and enlarged 4 fingerbreadths below the costal margin. No heart lesion was detected.

Laparotomy (W. F. W. S.) revealed many large yellow metastases in both lobes of the liver and a small solitary tumour of the ileum 6 feet from the ileocæcal valve. During palpation of the secondary deposits bronchospasm was noted by the anæsthetist. The ileal tumour was resected with end-to-end anastomosis.

Investigations. — The screening test of Sjoerdsma *et al.* (1955, 1957) for 5-hydroxyindole acetic acid (5-HIAA) in urine was positive. Three twenty-four-hour specimens of urine contained 277, 248 and 204 mg of 5-HIAA; chromatography of the urine for indoles revealed a preponderance of 5-HIAA, some indole acetic acid and tryptophan but no 5-hydroxytryptamine or 5-hydroxytryptophan (Dr. M. Sandler).

[1]Member of Scientific Staff, Medical Research Council.

Pathology (Dr. B. C. Morson).—A submucous tumour, 2 cm in diameter, protruded into the lumen of the ileum. On section the cut surface was pale yellow with hypertrophy of the muscularis externa within the tumour substance. Histologically it was a typical carcinoid. Silver impregnation and diazo staining showed a moderate degree of cytoplasmic granularity, the granules being distributed around the periphery of the cell clumps.

Discussion.—It is generally believed that in this syndrome flushing occurs only when a large bulk of tumour tissue is present. This patient has experienced flushing for twenty years and, despite replacement of probably half his liver substance by tumour tissue, his general health remains good. Asthma may occasionally be a feature (Waldenström and Ljunberg, 1955; Sircus 1956) and bronchospasm during anæsthesia has been noted before in these patients (Snow *et al.*, 1955; Sykes, 1956).

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Hæmopericardium Complicating Anticoagulant Treatment of Cardiac Infarct. — A. E. STEVENS, M.B., M.R.C.P. (for JOHN LISTER, M.D., M.R.C.P.).

History.—Two days before admission, this patient, who had previously been in good health, noticed a sudden severe left-sided and central precordial pain whilst walking. The pain was aggravated by deep inspiration, and was also felt in the upper arms. It was accompanied by much flatulence and persisted until admission on 11.1.60.

On examination.—Pulse 100, regular. Blood pressure 110/70. Temperature 99° F. No shock. Apex beat in the sixth left space 1 in. lateral to the mid-clavicular line. Heart sounds soft. No signs of failure. Shortly before admission a localized pericardial friction rub had been heard just medial to the nipple, but was never heard subsequently. No evidence of pulmonary œdema. Other systems normal.

Investigations (12.1.60).—ECG: Extensive anterior cardiac infarct (deep wide Q waves V 1–5 with raised ST segments and early inversion of T

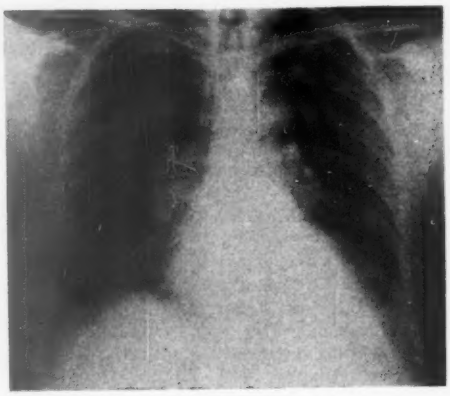

FIG. 1.—Chest X-ray 12.1.60.

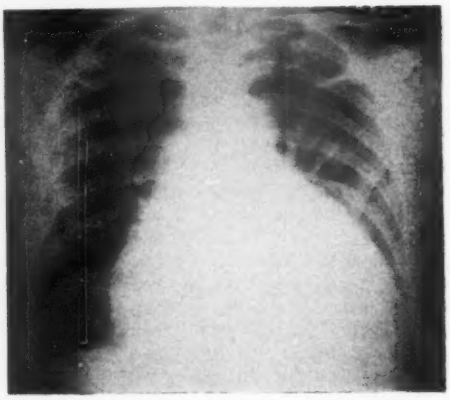

FIG. 3.—Chest X-ray 2.2.60.

waves in these leads). S.G.O.T. 68 units. S.G.P.T. 13 units. Hæmoglobin 109%. W.B.C. 9,800 (polys. 76%, lymphos. 16%, monos. 8%). E.S.R. 35 mm in one hour (Westergren). Chest X-ray (Fig. 1): lung fields clear; left ventricular enlargement.

Treatment and progress.—On bed rest and phenindione, progress was at first uneventful (*see* Fig. 2). On the morning of the eighteenth day after admission (29.1.60), he looked grey and ill. During the night he had vomited several times, but apart from some epigastric aching he made no specific complaints. The jugular venous pressure was raised to the angles of the jaw in the sitting position. The blood pressure was 80/60; he appeared to be anæmic. The apex beat was palpable in its original position and the heart sounds were clearly audible. There was no rub. There were rales at the lung bases, but no œdema.

At first it was thought that an extension of the infarct had occurred with consequent congestive failure. Later the same day, however, the patient had deteriorated further; he continued to complain of epigastric pain and his breath smelt as though he had had a gastro-intestinal hæmorrhage. Rectal examination was negative.

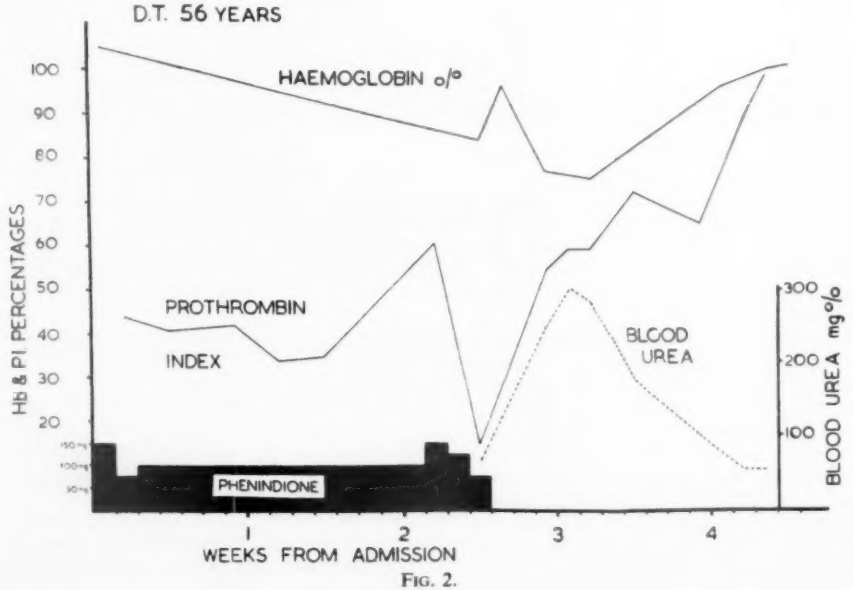

FIG. 2.

Investigations (29.1.60).—Hæmoglobin 84%. Prothrombin index 15%. S.G.O.T. 60 units. S.G.P.T. 50 units ECG no change.

Treatment.—Phenindione discontinued. 20 mg of vitamin K_1 was given immediately intravenously, followed by a slow 2-pint blood transfusion. Subsequently the blood pressure was maintained between 90 and 100 systolic by intramuscular and intravenous metaraminol.

Progress.—30.1.60: Hæmoglobin 77%. During the early part of the following week the patient's condition was critical. The urinary output on 30.1.60 was 6 oz; although this rose subsequently the blood urea on 2.2.60 had reached 300 mg%.

2.2.60: Chest X-ray (Fig. 3) showed a great increase in heart size with a shape suggestive of pericardial fluid. At this time, although the apex beat was readily palpated, percussion showed dullness immediately lateral to it. As the patient was by now improving, it was not thought advisable to attempt to aspirate the effusion. From this time the patient made an uninterrupted recovery. The jugular venous pressure gradually fell to normal and the cardiac outline returned almost to its original size. The blood urea fell by 11.2.60 to 55 mg%. Thirteen weeks after admission the patient was discharged to continue his convalescence at home.

Comment.—There seems little doubt that this patient had a hæmopericardium, although in the absence of paracentesis there is no absolute proof. Izzo *et al.* (1953) described 3 cases of hæmopericardium associated with anticoagulant treatment of cardiac infarction and gave details of a further 7 cases from the literature. Peyman (1958) mentions one presumed hæmopericardium occurring in similar circumstances, and Rose *et al.* (1953) describe successful pericardiotomy in such a patient. Of 3 cases with cardiac infarction and hæmopericardium described by Anderson *et al.* (1952) I was on anticoagulants, but it is interesting that the other 2, 1 of which was confirmed by post-mortem, were at no time on anticoagulants. Omitting the last 2, 9 out of 13 cases were fatal. In none of them was myocardial rupture found at post-mortem. Aaseth and Lange (1958) reviewed 1,229 post-mortems in fatal myocardial infarcts and collected 89 with hæmopericardium, comprising 81 with myocardial rupture, 3 with rupture of the aorta, and 5 for which there was no demonstrable cause. All the latter had been treated by anticoagulants.

Fatal hæmopericardium is also described as occurring during anticoagulant treatment of acute non-specific pericarditis (McCord and Taguchi, 1951) and dissecting aneurysm of the aorta (Brumfitt and Rankin, 1954). In both cases cardiac infarction had been incorrectly diagnosed. The unequivocal electrocardiographic findings rule out these possibilities in the case reported here. In retrospect, the presence at the onset of chest pain worsened by respiration suggests that pericarditis was more extensive than was indicated by the transient rub. With such a history, even in the absence of other evidence of pericarditis, caution in the use of anticoagulants is advisable.

Acknowledgments.—I thank Dr. John Lister for his kindness in encouraging me to report his patient, and Mr. Peter Fiske of the Photographic Dept., Canadian Red Cross Hospital for slides and photographs.

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Refractory Anæmia.—A. J. E. BRAFIELD, M.B. (for H. WYKEHAM BALME, F.R.C.P.).

W. W., male, aged 61.

November 1955: Admitted to Whipps Cross Hospital complaining of dyspnœa, lassitude and intermittent claudication. Hb 48%. Film normochromic with elliptocytosis. M.C.D. 7·3μ. Direct Coombs test negative. Reticulocytes 12%. Serum bilirubin 0·8 mg%. Fæcal urobilinogen 178 mg/100 gram fæces. Barium meal normal. X-ray chest normal. Marrow puncture very cellular. Normoblastic L : E=1·2 : 1. No response to iron, folic acid or vitamin B_{12}. Blood urea 48 mg%. Blood group A, Rh+. Fasting test meal: no free acid. Transfused and discharged with Hb 90%.

January 1956: Hæmorrhoidectomy.

June 1956: Readmitted. Hb 46%. Film normochromic with elliptocytosis and polychromasia. M.C.V. 105 cu.μ. M.C.H.C. 35%. Marrow biopsy as before. W.R. negative. Erythrocyte osmotic fragility normal. Fæcal urobilinogen normal. Direct Coombs test negative. No cold or warm hæmolysins or agglutinins. Ham's test and Donath-Landsteiner reaction negative. E.S.R. 22 mm/1 h (Westergren). Transfused with 3 pints of blood and cell survival studied by the Ashby technique. This subsequently proved to be normal. Discharged with Hb 70%, which thereafter rose steadily without treatment to reach 98% on July 22, 1956.

October 1956: Readmitted with Hb 42%, and appeared to respond to cortisone (three weeks'

course), thereafter Hb varied between 55% and 85% without further treatment.

May 1958: Admitted to St. Bartholomew's Hospital. Marrow hypercellular with a tendency to megaloblastosis. No myelofibrosis. Serum iron 194 μg%. Unsaturated iron binding capacity 106 μg%. 17-ketosteroids 9·8 mg/24 hours. Fæcal urobilinogen 460 mg per day. Other investigations confirmed previous findings. Studies with radioactive isotopes showed normal cell survival with marked impairment of iron turnover. Prednisolone, 30 mg per day, produced a prompt response and the patient was later discharged with Hb 98%. October 1958: Prednisolone reduced to 15 mg per day. July 1959: Prednisolone reduced to 10 mg per day.

December 1959: Readmitted with gross anæmia (Hb 32%), signs of cardiac failure, and purpura. Platelets 80,000 per c.mm. Marrow hypercellular and megaloblastic with very few megakaryocytes. Vitamin-A absorption test normal. Stools: occult blood negative. Prednisolone increased to 20 mg per day, plus folic acid 60 mg per day. Dramatic reticulocyte response (57%), followed by steady increase in Hb to 74%. Thereafter no further increase until parenteral vitamin B_{12} added, when Hb rose to 90% and has been maintained at that level. Serum vitamin B_{12} on admission 35μμg/ml.

Gastric Stricture following Ingestion of Ferrous Sulphate.—J. M. Davis, M.Chir., F.R.C.S.

History.—12.11.59: L. C., a girl aged 16 months, swallowed thirty of her mother's sugar-coated ferrous sulphate tablets. She received an emetic within ten minutes and a stomach washout within one hour before she was transferred to the care of Dr. S. Yudkin at the Whittington Hospital. Four hours after swallowing the tablets she became shocked and vomited blood-stained fluid; the vomiting continued for four days and necessitated intravenous therapy. Her condition then slowly improved and she was taking a normal diet when she was discharged home after sixteen days.

Four weeks later, six weeks after the initial poisoning, she was readmitted in a state of moderate dehydration caused by vomiting of increasing severity for the previous two weeks; the vomiting sometimes appeared to be self-induced by stimulation of the pharynx with her fingers. A barium meal (Fig. 1) showed a long stricture of the distal part of the body of the stomach and the proximal part of the pyloric canal; a little barium outlined a normal distal pyloric canal and a normal duodenal cap. The œsophagus was grossly distended and was obviously the cause of the self-induced vomiting.

Operation (31.12.59) was performed after rehydration for two days. There were four main findings; (1) A gastric stricture, about 5 cm long, as revealed by the barium meal. It would just admit a small probe. (2) Dense perigastric adhesions; the stomach was stuck to the left lobe of the liver and the lesser sac was partially obliterated. (3) Thickening and rigidity of the walls of the stomach; the incised wall measured 0·75 cm. This rigidity explained the failure of gastric distension and the gross œsophageal distension. (4) Extensive ulceration of the gastric mucosa proximal to the stricture, maximal in the region of the greater curvature and extending widely over the body of the stomach.

A wide, high, anterior gastrojejunostomy was performed. The post-operative course was complicated by prolonged paralytic ileus and a ruptured abdominal wound. However, she eventually made a good recovery and was discharged home after six weeks. A post-operative barium meal showed a good functioning stoma and a diminution of the œsophageal dilation. After three months her general condition remained good.

Comment.—8 previous cases have been reported in British journals (Crosskey, 1952; Ross,

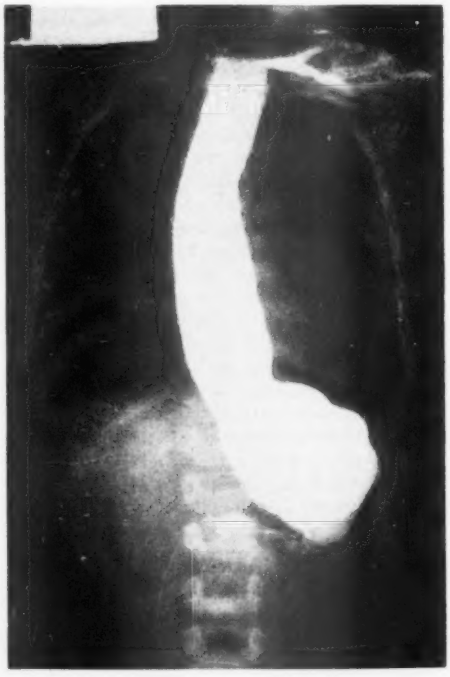

Fig. 1.—Gastric stricture caused by ferrous sulphate poisoning. Note the gross œsophageal dilatation.

1953; Forshall and Rickham, 1954; Elliott-Smith and Davies, 1954; Wilmers and Heriot, 1954; Shepherd, 1955). During the same period 28 cases of ferrous sulphate poisoning have been recorded. An additional case of gastric stricture has been reported from America (Warden *et al.*, 1958). The main features of 10 cases (the present case and the 9 previously reported cases) are shown in Table I.

TABLE I.—MAIN FEATURES OF 10 CASES OF FERROUS SULPHATE POISONING CAUSING GASTRIC STRICTURE

Age	13–36 months.	Average 21 months
No. of tablets	10–76	Average 32
Time for formation of stricture	3–7 weeks	Average 5 weeks
Treatment:	Medical	1 case
	Gastroenterostomy	4 cases
	Pyloroplasty	3 cases
	Gastrectomy	1 case
	Jejunostomy	1 case
Site of stricture	Pyloric canal	5 cases
	Body of stomach	5 cases
Dense perigastric adhesions	6 cases	
Result	2 died. 8 recovered	

An important feature of all the cases is the time-interval between the initial poisoning and the development of the stricture. This has led to a deceptive period of apparent recovery causing late diagnosis, malnutrition and dehydration in 6 cases. To avoid this all cases of iron poisoning should be kept under observation for six weeks and a routine barium meal performed at about this stage.

A unique feature of the present case is the gross œsophageal dilatation suggesting more extensive involvement of the stomach than has previously been reported.

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Diffuse Systemic Sclerosis Presenting as Infarction of Colon.—D. A. W. EDWARDS,[1] M.D., M.R.C.P., and J. E. LENNARD-JONES,[1] M.B., M.R.C.P. (for H. E. LOCKHART-MUMMERY, M.D., F.R.C.S., and F. AVERY JONES, M.D., F.R.C.P.).

Woman, aged 66. Housewife.

Admitted to St. Mark's Hospital as an emergency with a history suggesting intestinal obstruction. At laparotomy, the descending colon was found to be partially infarcted. The impaired blood supply to the colon was later shown to be one manifestation of a widespread collagen disorder.

[1]Members of Scientific Staff, Medical Research Council.

History.—For twenty years she has been troubled in cold weather by blueness of her fingers, without stiffness, blanching or paræsthesiæ and for ten years her feet have been sensitive to cold. For five years, since the age of 61, she has felt unwell, has had a poor appetite and has lost weight, suffering with increasing frequency from episodes of abdominal distension followed by profuse vomiting of brown fluid. She has eaten meals infrequently because "the food seems to take about seven hours to digest and I cannot look at food within six or seven hours of a meal", and found it necessary to drink with meals because her mouth has become dry, making solid food difficult to swallow. There have been no symptoms of dysphagia and no heartburn. There is no history of arthritis, dyspnœa on exertion, cough, or the appearance of subcutaneous nodules.

On examination.—The diagnosis of scleroderma was suggested by her mask-like face, with pursed mouth and stiff tethered skin making it impossible to evert the lower eyelid. The skin elsewhere was not obviously abnormal and there was nothing to suggest calcinosis. The finger tips were blue in a moderately cold environment but there was no loss of pulp substance.

Emergency laparotomy (H. E. L. M.).—The descending colon was plum-coloured and was judged nonviable; palpation revealed poor pulsation in all large blood vessels supplying the colon. Left hemicolectomy with transverse colostomy was performed.

Investigations.—Normal hæmoglobin, sedimentation rate, plasma proteins, blood urea, chest X-ray and X-ray of hands.

Gastro-intestinal motility: (*a*) X-ray findings: There was no œsophageal peristaltic activity so that when she swallowed barium in a head-down position it was not propelled uphill along the œsophagus, as it is in a normal person. When she swallowed barium in the standing position, the cardia was seen to be narrow and stiff. She experienced no difficulty in swallowing the barium and was unaware of the failure of the gullet to empty when upside down and of the restriction of flow at the cardia. The stomach changed very little in size and shape as barium was swallowed; most of the barium was still in the stomach eight hours later. Barium instilled into the first part of the duodenum failed to provoke the usual contraction. The duodenal loop was widely dilated (Fig. 1) and barium trickled slowly along it into the small intestine. Irregular dilatation of small intestinal loops could be seen and almost all the barium was still present in the small bowel after twenty-four hours. Barium instilled through the colostomy outlined a large sacculated and

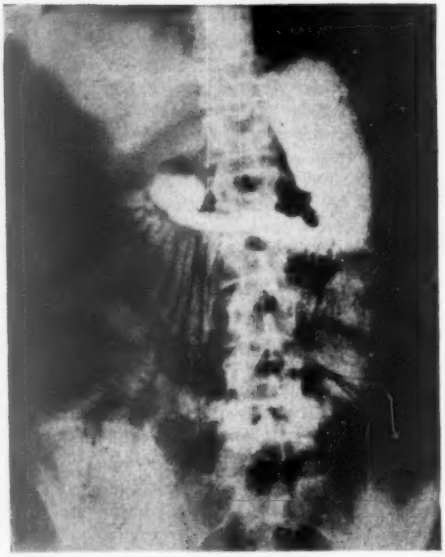

FIG. 1.—Barium meal showing dilatation of the duodenal loop and small intestine.

immobile right colon. (*b*) Manometric findings: The changes of pressure produced by muscular activity of the wall of the œsophagus, duodenum and transverse colon were recorded by miniature balloons (7 × 10 mm). There was complete loss of muscular activity in the body of the œsophagus. No cardiac sphincter could be demonstrated but there was some narrowing of the lumen at the cardia, which did not relax on swallowing, suggesting the presence of a fibrous structure at this point. The muscular activity of the duodenum and colon was grossly reduced (Fig. 2).

Intestinal absorption: The *d*-xylose excretion test was normal suggesting that there was no gross lesion of the intestinal mucosa. The rate of absorption of ^{131}I-labelled fat was slow but the total fat absorption was normal.

Pathology of operation specimen (Dr. B. C. Morson).—The wall of the colon was thinned with loss of haustration; the mucosa was ulcerated in some places. Histological examination revealed intimal proliferation of medium-sized arteries leading to gross reduction in lumen, patchy replacement of circular muscle by collagen and evidence of chronic ischæmia as judged by the atrophic mucosa with superficial ulceration (Fig. 3).

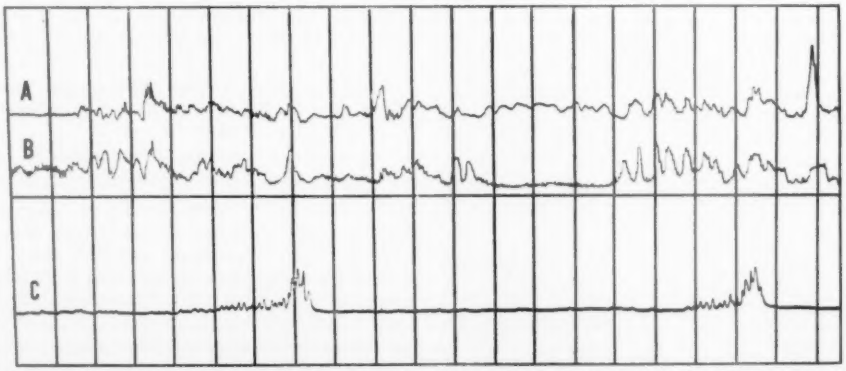

FIG. 2.—Upper tracings (A and B) show normal colonic activity. The lower tracing (C) illustrates the remarkable lack of muscular activity in the patient's colon. The tracings were obtained with miniature balloons (7 × 10 mm); vertical lines indicate minute intervals. Normal by courtesy of Dr. A. Connell.

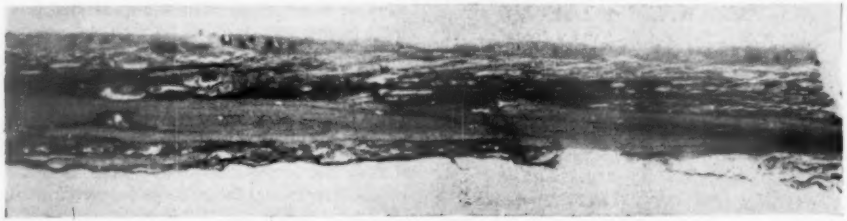

FIG. 3.—Photomicrograph of the wall of the patient's colon. Collagen fibres, stained black, are seen partially replacing smooth muscle, stained grey, the mucosa is atrophic.

Discussion.—Some recent reviews of diffuse systemic sclerosis (scleroderma) are listed below.

In this case there seems little doubt that the impaired blood supply of the colon was due to the intimal proliferation in the arteries, a characteristic feature of systemic sclerosis. A somewhat similar case has been described by Lushbaugh *et al.* (1948). Our patient illustrates how extensively this disease may involve the gastro-intestinal tract, without much involvement of the skin or other organs, and how well the gut involvement may be demonstrated by radiological and manometric studies of motility. The inertia of the whole intestinal tract is presumably the result of replacement of smooth muscle by collagen as was found in the portion excised.

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Swollen Calf for Diagnosis. Possible Vascular Hamartoma.—R. S. MURLEY, M.S., F.R.C.S.

Mrs. P. H., aged 43.

History.—Swelling of the left calf for as long as she can remember. About November 1959 began to notice "fulness" of left leg and prominent superficial veins. The calf is noticeably softer in the morning and tends to harden during the day. The left foot does not suffer from the cold so much as the right. The only previous trouble followed birth of her two children fifteen and ten years ago when the leg became more swollen and painful within a few hours of delivery and this persisted for about a week.

On examination.—A fit woman. Right leg normal. Left leg: No increase in length. Firm and uniform enlargement of whole calf. Circumference 17½ in. compared with 14 in. on the right. Prominent veins on left thigh and dorsum of foot (Fig. 1). Left foot warmer than right after exposure. No bruit audible in foot or leg.

Investigations.—Chest X-ray normal. Plain X-ray legs: Soft-tissue swelling in left calf between deep fascia and deep muscular layers. Density suggests that this could be a subfascial or intramuscular lipoma.

Left femoral arteriogram (Dr. K. Ashcroft): Normal main arteries but rapid transit into dilated and tortuous calf veins which appear to be situated in or near to surface of tumour. A further series with more rapid changing of films failed to demonstrate any abnormal arteriovenous communication or angiomatous circulation in leg or ankle. Tortuous veins in foot but no arteriovenous shunt seen. Deep veins not filled in any of these films, but subsequent ascending venogram with superficial tourniquet applied showed normal deep veins.

Discussion.—The calf tumour is most likely to be a lipoma or hæmangiolipoma. The dilated and tortuous superficial calf veins do not appear to be part of the tumour circulation although their rapid filling suggests a possible arteriovenous shunt in the foot. Against this last suggestion is the normal length of leg, absence of audible bruit and failure to demonstrate any vascular communication in the arteriograms.

POSTSCRIPT (24.9.60).—Subsequent exploration on 7.6.60 confirmed the diagnosis. The tumour was reported as a hamartomatous lipomatosis of skeletal muscle with overgrowth of vessels (Dr. J. I. Pugh).—R.S.M.

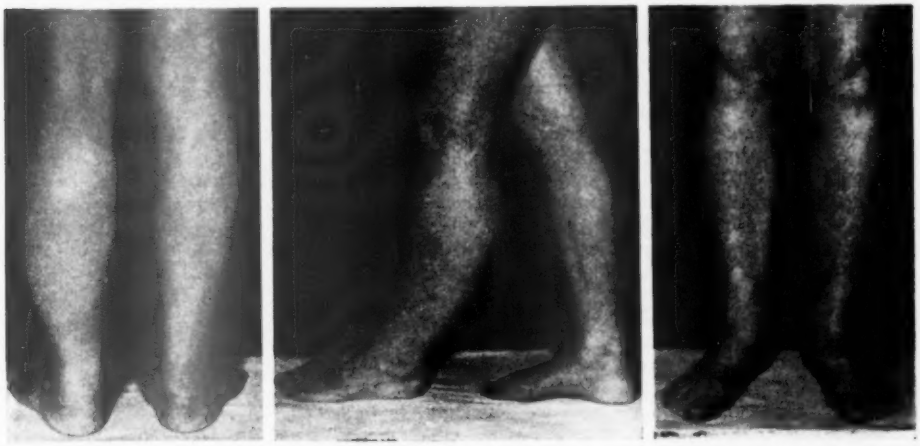


FIG. 1.—Showing swelling of left calf, normal length of leg and prominent veins on dorsum of left foot.

? Polyarteritis Nodosa.—LEO GILCHRIST. M.D., M.R.C.P., D.P.M.

Miss E. C., aged 34. Admitted to Farnborough Hospital on 13.3.58 with five-day history of headache, sore throat, pains in limbs, and erythema mutliforme.

Past history.—Treated for tuberculous spine in 1955–56. No personal or family history of allergy.

On admission.—Temperature 99·8° F, pulse 120, respiration 20. C.N.S.: slight neck stiffness and absent knee-jerks. Blood pressure 110/80. Her pyrexia continued, reaching a peak of 104° F on 14.3.58, and subsiding on 8.4.58. Her wrists and fingers became painful and swollen, and subsequently all the larger joints were affected. 28.3.58: Exudates appeared on left fundus. 2.4.58: Suddenly acute breathlessness with pain in right chest. She was given 100 mg hydrocortisone intravenously followed by prednisone, streptomycin, isoniazid, and Terramycin, but required an oxygen tent continuously for three days. 11.4.58: Exudates and small hæmorrhages appeared in both fundi. 13.7.58: She had a recurrence of her joint pains when her prednisone was temporarily omitted. She was fit for discharge a month later.

Special investigations.—On admission her blood count was normal. 25.3.58: Hb 9·9 g/100 ml (67%) W.B.C. 14,000 (neutros. 12,000, eosinos. 280). 8.4.58: Hb 11·9 g/100 ml (81%). W.B.C. 21,000 (neutros. 18,270, eosinos. 630). Subsequent counts were all normal.

Blood cultures, and agglutination reactions to *Salmonella typhi*, *Sal. paratyphi A*, *B* and *C*, and *Br. abortus* were all negative. Complement-fixation tests to influenza A and B, the adenopharyngoconjunctival group, Q fever, and psittacosis were also negative, and the anti-streptolysin titre was normal.

31.3.58: No L.E. cells were seen in the blood; muscle biopsy for polyarteritis nodosa was negative. Electrophoresis showed a total protein of 5·3 g/100 ml, with deficient albumin, and an increase in the α_1 and α_2 globulin fractions.

14.3.58: Urine showed some albumin. No pathogenic organisms isolated from sputum.

Chest X-rays.—15.3.58: Lung fields clear. Heart shadow normal. 29.3.58: Lung infiltrations showed a bat's wing distribution typical of pulmonary œdema. Appearances consistent with acute stage of collagen disease. 14.4.58: Bat's wing opacities had largely cleared, but patchy shadowing had spread to the periphery of the lungs, especially at the bases. 4.7.58: Lung fields clear.

Subsequent follow-up as an out-patient.—23.8.59: Mistiness of vision in right eye for three weeks. 1.12.59: Paræsthesiæ in right leg for two and a half months. She is otherwise well apart from occasional "rheumatism" in the neck and joints. It has not been possible to reduce her prednisone below 10 mg a day.

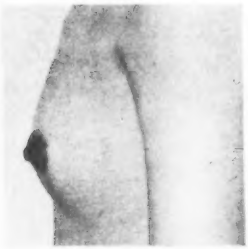
Discussion.—Although there was no pathological confirmation, the clinical course of the disease, the fact that no bacterial cause was found, and the response to steroids, favour a diagnosis of polyarteritis nodosa. If so, she belongs to the group with lung involvement (Rose and Spencer (1957) *Quart. J. Med.*, **26**, 43).

Sponge Implants for Flat Breasts.—PATRICK CLARKSON, F.R.C.S.

The patient, a girl of 23, was referred by Dr. David Stafford-Clark because she was so distressed by her flat bosom. She had in the past been diagnosed as a chronic hysteric with an anxiety state and been said to have a psychopathic personality. There were two questions: (*a*) Was plastic surgery justified? (*b*) If so, what method should be used?

(*a*) Plastic surgery is clearly justifiable if the operation is safe. Many people do not understand the profound misery suffered by young women with inadequate breast development, which often leads them to avoid social life and recreation. Also in marital crises the woman may blame her flat chest, and it is true that some husbands do mind quite a lot about this. When the loss of breast form follows childbirth and lactation the mother may blame the child for "ruining my body"; such an attitude disturbs family relationships. In general flat-chested women feel in some way inferior. In this patient such feelings were marked, and for a woman of her education and class she had an entirely abnormal attitude to men and to social life. In her case Dr. Stafford-Clark and I both felt plastic surgical treatment was fully justified even if complete freedom from long-term risks could not be guaranteed (Fig. 1).

(*b*) The choice of method for the production of a breast prominence rests between the use of autogenous tissues (dermo-lipomatous flaps or free grafts) and the use of foreign body sponges. Clearly the use of autogenous tissues is preferable if they are adequate and reliable. But they are not. Certainly some patients can have a reasonable-sized bosom restored by the use of local flaps of dermis plus fat; but the more widely used dermo-lipomatous free grafts from the buttocks are limited in size, absorb very largely and often asymetrically. I have used dermo-lipomatous grafts for eleven years and have had only one persistently satisfactory result; but this was not a large restoration. This adverse opinion of these buttock free grafts is shared by Conway and Smith (1958), Barrett Brown and Moore (1952), Edgerton and McClary (1958) and Harris (1957).



←FIG. 1.—Pre-operative state.

FIG. 3.—Post-operative state after replacement of polyvinyl sponge with the softer polyurethane sponge. →

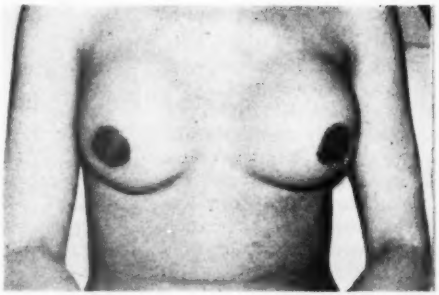


FIG. 2.—Polyvinyl sponge removed after one year showing 1 cm peripheral area of active benign fibrous tissue in growth.

The inadequacy of the dermo-lipomatous graft led some plastic surgeons in America to explore the safety of plastic sponges. It was not until polyvinyl alcohol had been used for ten years, and after a number of reports on its inertness, that I felt it justifiable to start a limited trial of this sponge in cases with marked psychological implications. The outstanding question is that of its possible carcinogenicity. There is no doubt about the relative inertness of polyvinyl alcohol as regards inflammatory reactions in the tissues. Edgerton, Barrett Brown and Harris describe it as being of lower carcinogenicity than cellophane or polythene. It is a resilient, inert sponge readily cut into various moulds. It has been used in some of the most reliable centres in America for ten years without report of any tumours; but if there is to be any tumour load in human beings its incidence will only be known after twenty to twenty-five years. Edgerton indeed believes that the presence of an implant sponge behind the breast tissues will make any spontaneously developing carcinoma in that breast more readily detectable. It has been claimed that it is one of the least carcinogenetic foreign bodies; nevertheless it is certain that some tumour load does occur in rats (Horning, 1959; Dukes, 1959).

Polyvinyl alcohol implants become unduly hard in the breast—as hard as a horsehair mattress. I have used these implants in about 15 patients over the last two years, most of whom are unconcerned about the increased firmness. This girl was keen, when told that polyurethane sponges were softer, to have the polyurethane sponge substituted for polyvinyl alcohol. This was done on 28.1.60 (Fig. 2), and the result is a breast similar in form to that of the polyvinyl alcohol. It too is firmer than normal but feels "comfortable" and "part of herself"; she has full sensitivity of the nipples. She is quite emphatic about her satisfaction in the operation and could never contemplate reversion to her flat-chested state; she now mixes freely in social events (without a coat on) and for the first time indulges in such recreations as swimming The polyurethane sponge on the left side, however, intermittently discharged after three months *in situ;* its future fate is doubtful. (Fig. 3.)

One application of these implants in the treatment of the flat chest which could be of special psychological help is its insertion after simple or radical mastectomies. I have treated 2 such patients, but only as secondary procedures. Polyetheron sponge is an alternative polythene plastic which is softer but still firmer than normal breast.

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Rheumatic Tricuspid Stenosis, Cardiac Cirrhosis.—G. H. APTHORP, M.B., M.R.C.P. (for G. W. HAYWARD, M.D., F.R.C.P.).

Mrs. R. D., aged 46.

As a child she suffered from rheumatic fever and led a restricted childhood due to dyspnœa.

1935: She was married and a few months later noticed progressive swelling of the abdomen, and

her ascites has been tapped since then.

1954: Totally incapacitated by dyspnœa; admitted to St. Mary's Hospital. Exploration of the mitral valve showed stenosis with a considerable regurgitant stream. Some splitting of the medial cusp was carried out. After operation her dyspnœa was considerably improved and the ascites slightly improved.

1958: Again incapacitated by ascites; admitted for consideration of a hepatic by-pass operation.

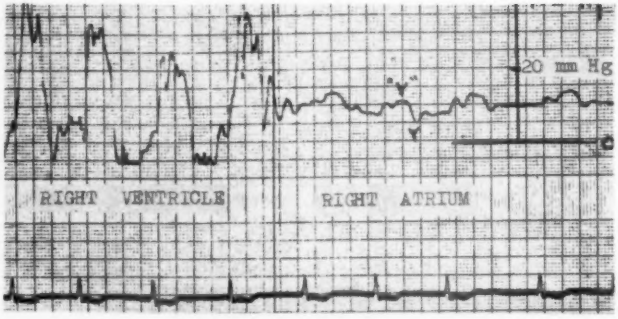

FIG. 1.—Withdrawal pressure tracing across the tricuspid valve showing pressure gradient during ventricular diastole.

On examination.—No jaundice; gross peripheral œdema, ascites, and pleural effusions. Blood pressure 150/90. The radial pulse showed atrial fibrillation and the neck veins were engorged to the angle of the jaw with a dominant "V" wave. The heart signs were those of mitral incompetence and stenosis and, in addition, there was a loud systolic and diastolic murmur in the tricuspid area increasing with inspiration (Fig. 1) and indicating tricuspid stenosis and incompetence (Gibson and Wood, 1955). The abdomen showed a considerably enlarged liver.

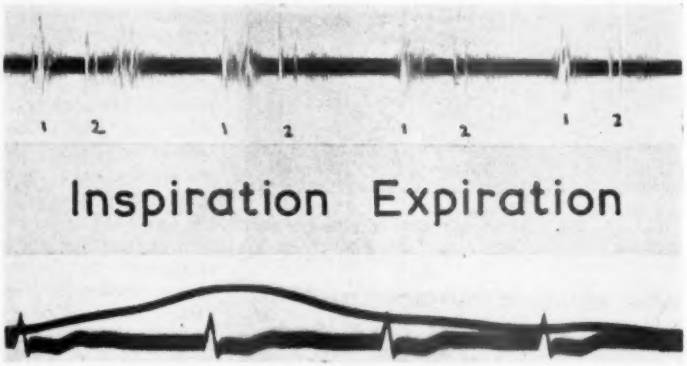

FIG. 2.—Phonocardiogram (Dr. Malcolm Towers) showing increase in both diastolic and systolic murmurs in tricuspid area during inspiration.

Investigations.—Cardiac catheterization showed normal pulmonary pressure at rest but a considerable rise of the pulmonary capillary pressure on slight exercise. The presence of tricuspid stenosis was confirmed by an 8 mm diastolic pressure gradient on withdrawal across the tricuspid valve (Fig. 2). Liver function tests normal.

Treatment.—After twenty-five years' medical treatment the patient asked that surgical treatment should be considered.

Hepatic by-pass operation in the presence of tricuspid stenosis by increasing the venous return is likely to raise still further the venous pressure and, therefore, the back pressure on the liver.

Tricuspid valvotomy: Since tricuspid stenosis is nearly always associated with incompetence and valvotomy may well replace the stenosis by incompetence, the patient is likely to be made worse by this operation unless simultaneously the work of the right ventricle is reduced by a successful mitral valvotomy.

Mitral valvotomy: As Angelino *et al.* (1959) have shown, successful mitral valvotomy will reduce the degree of tricuspid incompetence. In this patient any increase in the degree of mitral incompetence will increase the work of the right ventricle and the degree of tricuspid incompetence and, therefore, the back pressure on the liver.

She is considered unsuitable for operation until a successful method of repair of mitral incompetence is available which could be combined with tricuspid valvotomy.

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The following cases were also shown:

High Intestinal Obstruction due to a Congenital Diaphragm of the Duodenum.—C. N. HUDSON, F.R.F.P.S. (for IAN P. TODD, F.R.C.S.).

Idiopathic Cardiomegaly.—T. GEBBIE, M.B. (for H. WYKEHAM BALME, F.R.C.P.).

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Lancet (1958) **1**, 525

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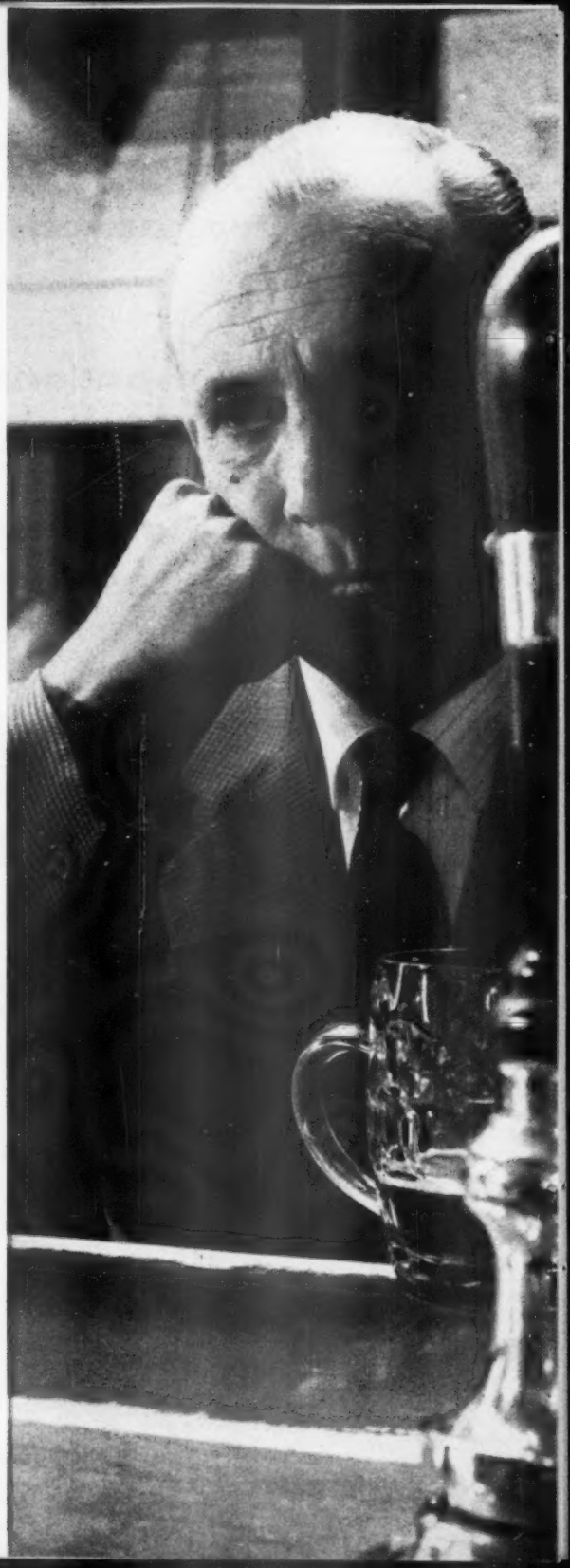

BPL.3

Section of Orthopædics

President—DAVID TREVOR, M.S.

Meeting
April 5, 1960

Traumatic Spondylolisthesis of the Sacrum.—RODNEY SWEETNAM, F.R.C.S. (for H. OSMOND-CLARKE, F.R.C.S.).

A small proportion of cases of lumbosacral spondylolisthesis are caused by violence. The patient reported is, however, an example of what must be an extremely rare variety of traumatic spondylolisthesis, for in this case the body of the first sacral segment slipped forward on the remainder of the sacrum below. I have been unable to find any previous account of such an occurrence in the English literature.

History.—A boy of 14 was bending forward when a falling pole 9 in. in diameter struck him across the low back.

He was admitted to hospital and found to have a severe transverse fracture (separation) of the sacrum with forward displacement of the body of S.1 together with a thin plate of bone from the upper surface of the segment below (Fig. 1). One lumbar transverse process was also fractured.

The only signs of nerve damage were anæsthesia along the outer border of the right foot and an absent ankle reflex on the same side.

Attempts at reduction by heavy skin traction on both flexed legs failed; indeed, during this period and shortly afterwards, further slipping occurred, callus appeared and the body of S.1 eventually united in front of the lower part of the sacrum (Fig. 2).

It is now five years since the accident. He has no pain whatsoever and is a keen footballer. Examination shows the typical deformity of severe spondylolisthesis but back movements are otherwise free and painless. The only remaining indication of nerve damage is absence of the right ankle reflex.

Comment.—There are three features of interest in this case.

Traumatic sacral spondylolisthesis must be extremely rare, for I can find no record of previous description. In the scanty literature on fractures of the sacrum most authors agree that, in transverse fractures of the bone, the lower portion is displaced forwards in relation to the

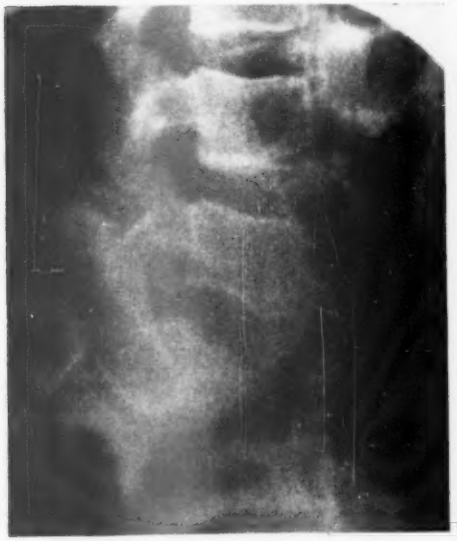

FIG. 1.—Forward displacement of S.1 on the segment below immediately after injury.

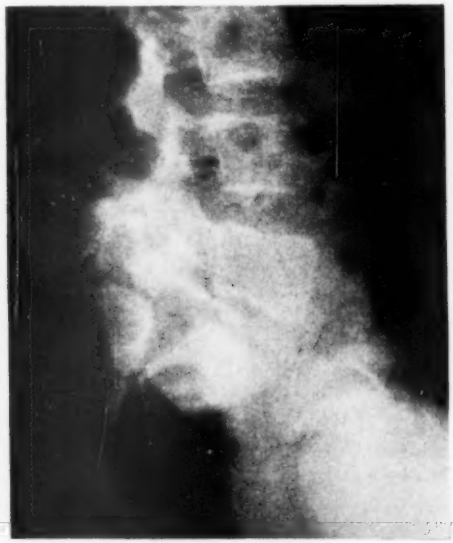

FIG. 2.—One month later. Further forward and downward slipping has occurred in spite of attempted reduction.

segment above. In this patient the first sacral segment together with its articular facets above, and a fragment from the body of S.2 below, became separated from the lateral masses and displaced forwards; later, further forward and downward slipping occurred, and finally fusion took place in front of the lower sacrum.

The second interesting feature is the total failure to reduce the displacement even in the early stages, by powerful leg traction.

Finally, but by no means of least interest, is the extraordinary lack of nerve damage in spite of severe and rapid displacement.

Actinomycosis of the Finger.—W. M. WEARNE, F.R.C.S.

History.—A. S., a man aged 46, lacerated his right index finger on an adversary's tooth when involved in a fight. The wound was on the dorsum of the proximal interphalangeal joint. The wound was dressed the following day and he commenced a short course of penicillin injections. The wound healed rapidly, but the finger remained swollen and painful.

Three months later the stiffness and swelling of the finger had not subsided. On examination there was swelling of the proximal segment of the finger and marked limitation of flexion of both interphalangeal joints. An X-ray showed a small area of rarefaction in the head of the proximal phalanx. A course of heat treatment and active exercises was commenced. During this treatment the finger became increasingly swollen and red.

A month later a fluctuant area appeared on the dorsum of the proximal segment of the finger. An X-ray then revealed a punched-out area of bone destruction in the head of the proximal phalanx with surrounding rarefaction and erosion of the adjacent cortex (Fig. 1). An incision was made into the fluctuant area under general anæsthesia (Fig. 2). Thin pus, containing small white flecks, was released. *Actinomyces israeli* was identified both on direct examination and on culture of the pus (Fig. 3).

Following identification of the organism, the patient is being treated with a prolonged course of massive dosage of penicillin. At present he is receiving injections of 5 mega units of Triplopen on alternate days.

Ten weeks after incision the swelling had subsided. The range of movement of the finger was almost full and the skin well healed. An X-ray showed recalcification of the proximal phalanx.

Penicillin therapy was maintained for a total of seventeen weeks with an excellent clinical result.

Actinomycosis of the finger is a rarity. Under the title of "Actinomycosis from Punch Injuries", Burrows reviewed the literature in 1945. He presented one personal case and quoted one reported by Cope (1915) and one by McWilliams (1917). In each case the infection had occurred

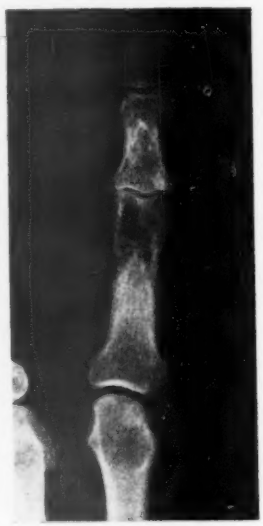

FIG. 1.—X-ray of the finger.

FIG. 2.—Appearance of the finger after incision and drainage.

FIG. 3.—Swab taken from the wound. The swab is submerged in liquid meat medium. The white nodules on the swab are the so-called "sulphur granules" which have increased in size after several days' incubation.

after the person had lacerated a part of his hand on an adversary's tooth. As *Actinomyces israeli* is regarded as a normal inhabitant of the human mouth, there seems little doubt that the infection occurred at the time of injury.

Massaglio (1904) reported a case of actinomycosis of the finger which arose without antecedent pathology.

I wish to thank Mr. David Trevor for permission to present this case, and the Department of Clinical Photography at Charing Cross Hospital, London, for the clinical photographs.

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The following cases were also shown:

Reconstruction of the Thumb: (1) By Tube Pedicle and Bone Graft, with Islet Neurovascular Pedicle Graft from Fourth Finger. (2) By Littler Type Pollicization.—Mr. PATRICK CLARKSON.

Treatment of Gross Multiple Congenital Deformities.—Mr. R. H. METCALFE.

Bilateral Congenital Posterior Dislocation of the Radial Heads.—Mr. A. C. HUME (for Mr. H. OSMOND-CLARKE).

Chondroblastoma of the Femoral Head.—Dr. J. E. MILLER (for Mr. H. OSMOND-CLARKE).

(1) Tenolysis of Flexor Longus Pollicis. Polythene Film Used to Prevent Re-adhesion. (2) Firework Explosion Injury to Hand. (3) Flexor Tendon Injury: Result of Immediate Repair.—Mr. C. R. MCCASH.

Aneurysmal Bone Cysts.—Mr. H. PIGGOTT (for Mr. PHILIP NEWMAN).

(1) McKeever Arthroplasty of the Knee-joint. (2) Congenital Recurrent Dislocation of the Patella.—Dr. A. MANZONI.

Loose Body in Hip-joint.—Mr. G. RIGBY JONES.

Case for Diagnosis. Multiple Skeletal Lesions. ? Neurofibromata. ? Inflammatory.—Miss D. M. H. COTHAY (for Mr. J. D. WILSON)

Meeting
May 7, 1960

MEETING AT THE HARLOW WOOD ORTHOPÆDIC HOSPITAL, MANSFIELD, NOTTS

CASES, including the following, were demonstrated by Mr. A. N. BIRKETT, Mr. J. P. CAMPBELL, Mr. C. CHAPPLE, Mr. J. P. JACKSON, Mr. S. A. S. MALKIN, Mr. A. B. MORRISON, Mr. E. A. NICOLL, Mr. R. G. PULVERTAFT and Mr. W. WAUGH:

Tendon Graft for Divided Profundus with an Intact Sublimis.

Tendon Graft to Replace Divided Profundus and Sublimis Tendons After a Long Delay.

Ruptured Central Slip—Extensor Tendon.

Division of Tendons and Nerves at Wrist Level.

Opposition Transplant.

Arthrodesis of Wrist in Children.

Arthrodesis of Shoulder.

Osteotomy of Tibia for Osteoarthritis of the Knee.

Osteotomy of First Metatarsal for Hallux Valgus.

Cancellous Insert Grafts.

Congenital Pseudarthrosis of the Tibia.

Quadricepsplasty.

Osteoarthritis of Hip. Trochanteric Forage.

Short Papers were read, of which summaries appear overleaf.

Recurrent Dislocation of the Shoulder

By A. N. Birkett, F.R.C.S.

Blundell Bankart was amongst the earliest workers to demonstrate the essential pathological change in recurrent dislocation of the shoulder. He was convinced that the main cause was the shoulder being forced forward with the arm held to the side; this caused shearing of the glenoid labrum. However, it does seem almost certain that the position of the arm is of little importance provided the force is exerted either from the back or from the side along the axis of the limb. This forces the humeral head against the glenoid stretching the capsular structures at the front of the joint. If the force is great a tear occurs and this is frequently of the cartilaginous rim from the glenoid. The joint is then liable to subluxation so that when the shoulder is suddenly externally rotated the humeral head may leave the articular surface of the glenoid and on internal rotation a complete anterior dislocation occurs.

Of the many surgical operations devised to prevent recurrent dislocation of the shoulder the earliest sling and tendon operations had little scientific basis and later operations, such as the Putti-Platt and Bankart, limited external rotation of the joint.

The only operation using any other principle is the anterior bone block. Such a block screwed in front of the glenoid rim extends this forward so that external rotation of the shoulder can take place without the humeral head dislocating. In this operation a substantial portion of bone is obtained from the iliac crest and fixed in front of the glenoid rim by two vitallium screws. The articular aspect of the bone is carved to continue, as far as possible, the curve of the glenoid cup. The subscapularis tendon is reinserted across the front of the graft but no repair of the capsule is necessary. The only post-operative treatment required is rest in a sling. Mobilisation of the shoulder under the guidance of a physiotherapist is started when the wound is healed and full movement of the shoulder is usually obtained in three to four months.

The age of the 20 patients on whom this operation has been carried out shows that recurrent dislocation of the shoulder is essentially a condition of youth. 7 had had a first dislocation at 19 years or less and 11 between 19 and 25 years. Dislocation did not, however, always occur at the initial injury. One patient of 22 years had a hammer dropped on his shoulder while at work and dislocation did not occur until he was swimming some weeks later; it recurred about twenty times before he was operated on at the age of 43 years. Another at 19 years fell on his shoulder with the arm at his side; three weeks later his shoulder dislocated when he was reaching backwards with the arm abducted; seven years later a further dislocation occurred while he was paper-hanging at home.

The above suggests that the Bankart lesion may be caused by an accident which does not produce a complete dislocation but produces a tearing of the glenoid lip. Once such a tear has occurred the first dislocation may merely aggravate a well-established condition so that enforced rest does not produce future security of the joint.

Titanium in Treatment of Fractures of the Femoral Neck

By J. P. Campbell, F.R.C.S.Ed.

Fractures of the neck of the femur still merit the title of the unsolved fracture. Any operation advocated should be simple, easily and quickly performed and produce a minimum of shock. The size of the problem was illustrated by the fact that 96 cases of fracture of the femoral neck had been admitted to Nottingham General Hospital in six months. The average age was 77 years with as many patients over 90 as there were under 65 years. Of the 96 cases admitted 39 had serious pre-existing diseases of which the respiratory disorders took first place and cerebral vascular lesions second.

The treatment of basal fractures had been by internal fixation by a pin and plate except in a few cases where operation had been contra-indicated and these had been treated by traction. The results of both methods were satisfactory.

The medial fractures of the femoral neck in the younger age group had been treated by reduction and internal fixation by a Smith-Petersen pin but in the over 65s Smith-Petersen pinning had given disappointing results and the method advocated was either by osteotomy and internal fixation with a titanium plate of the Harlow Wood pattern or the replacement of the femoral head by a titanium prosthesis of the Pembury type.

Titanium has been in use for the past two years and, out of 85 cases of varying types, in only one had there been a reaction necessitating removal of the plate.

Titanium prostheses for femoral head replacement had been in use for the past twelve months and had given satisfaction. The patient started gentle weight-bearing with crutches twelve to fourteen days after operation when the wound was soundly healed.

Arthrodesis of the Wrist in Children

By J. P. JACKSON, F.R.C.S.

ARTHRODESIS of the wrist is carried out in children so that splints may be removed, tendon transfers carried out and the patients may become adapted to the stiff joint early in life.

There are three reasons why this may not be frequently done. Firstly it may be difficult to achieve, secondly it may interfere with growth, and thirdly deformity may recur in growing bone. In a series of 11 cases 9 have fused satisfactorily suggesting that this is not difficult to achieve. It should be recognized that the affected wrist is likely to be smaller due to the disease process. Provided that the central epiphysis and its blood supply remain intact it is likely that growth will continue. So far as is known, the carpal bones grow by concentric rings of bone being laid down around a central epiphysis. This epiphysis is supplied by a single vessel which probably enters the bone from the anterior surface.

The technique used has been to remove all the articular cartilage from the carpal bones and the distal surface of the radial epiphysis. This spares the central epiphysis and since the anterior surface is not touched the blood supply remains intact. No bone is added and the wrists are put in plaster for three to four months.

One patient remained unfused in both wrists, possibly due to immaturity of the bone as the patient was only 5 years old, or to lack of compression. There was almost complete paralysis in both wrists and fingers.

Comparable X-rays taken immediately following operation and at follow-up show that in all cases the width and thickness of the fused mass has increased. In 50% of the cases the length, however, has decreased suggesting that this was due to muscle pull producing compression.

There is no doubt, therefore, that satisfactory fusion can be obtained and that growth will occur following this. Provided adequate muscle balance is obtained, no deformity will recur in the growing bone.

Morbidity in Bone Donor Sites

By H. HARROP-GRIFFITHS, F.R.C.S.

53 patients who have had autogenous bone grafts carried out were reviewed to determine whether there were late disabilities at the donor sites. The ilium had been used in 25 cases and the tibia in 28.

In 3 cases the posterior part of the crest of the ilium was used. The incisions were along the line of the cutaneous nerves and there were no symptoms referable to the skin. There was no appreciable bone defect; the area was well covered by muscle and fat.

In 22 cases where the anterior crest was used, the incision was along the crest and had avoided the cutaneous nerves. In 7 cases where the outer table only had been used, 4 had marked recession of the origins of gluteus medius and tensor fascia lata and 3 had a minor degree of recession. There was no functional disability.

Where bone had been removed by wedge resection and the anterior superior iliac spine left, all 4 cases had disabilities due to this prominence.

In 12 cases where bone had been removed in parallel cuts, 7 were featureless. There was 1 small hernia and 4 in which the tubercle of the ilium had been left as a prominence.

In the tibial cases it was found that the incision was the main factor producing complications. These complications were either neural or venous. The neural complications were due to section of the radicals of the saphenous nerve resulting in an area of reduced sensation, poor-healing skin and a burning feeling lateral to the scar, or were due to involvement of the saphenous nerve, itself, in scar tissue.

The venous complications were swelling after exercise. This was due to section or subsequent fibrosis involving the long saphenous vein or perforator veins. Of the 28 cases in this group, 17—that is 61%—had neural or venous disability or a combination of both.

It was suggested that the incision should lie over the tibialis anterior muscle, that is, in the interneural area, half an inch lateral to the anterior border of the tibia. Deep fascia can be incised in the same line and dissected up in continuity of the periosteum over the subcutaneous surface of the tibia.

There were no disabilities resulting from the method of bone removal apart from 1 in which the tibia fractured at its lower third.

The Late Treatment of Profundus Division Within the Digital Theca

By R. G. PULVERTAFT, F.R.C.S.

THE choice of treatment lies between arthrodesis of the terminal interphalangeal joint, tenodesis or restoration of tendon action by tendon grafting. The decision depends upon age, state of the finger, the occupation and the wishes of the patient. Tendon grafting is an operation of some magnitude for a comparatively small disability and should only be undertaken by the surgeon experienced in this work and when the patient is determined to seek perfection.

Analysis of 33 consecutive cases operated upon by tendon grafting during the past eighteen years reveals 4 failures. Of the remaining 29 cases, 92% attained 30 degrees or more flexion range at the terminal interphalangeal joint and 55% reached to within half an inch or less of the distal palmar crease. In no case was the finger harmed by surgical intervention.

(A film demonstrating the technique of the operation was presented.)

Tibial Osteotomy for Osteoarthritis of the Knee

By J. P. JACKSON, F.R.C.S., and W. WAUGH, M.Chir., F.R.C.S.

OSTEOARTHRITIS of the knee is sometimes associated with a lateral (valgus or varus) deformity. When there is disabling pain but a good range of movement correction of this deformity by osteotomy is a logical procedure. The joint is realigned so that the forces of weight-bearing are more evenly distributed and no longer concentrated in the medial or lateral compartment.

In a valgus knee the deformity largely occurs in the lower end of the femur so a supracondylar osteotomy would seem indicated. In 4 patients (5 knees) this has been carried out but in each case there was serious restriction of movement after operation. When, however, the deformity is varus, osteotomy through the upper tibia is correct since the angulation occurs in this part of the bone. If this osteotomy is done for valgus the leg is made to look straight but the line of the knee-joint remains oblique to the horizontal plane. In spite of this theoretical objection the operation improves the stability of the joint and relieves the strain on the medial ligament.

9 patients (10 knees) with painful osteoarthritis have had an upper tibial osteotomy: 6 for valgus and 4 for varus deformity. The average age was 60 years and the average follow-up forty months. All were substantially relieved of pain and all except one (who had both knees operated on) recovered more than 90 degrees of flexion. There were no vascular complications. A ball and socket type of osteotomy through the cancellous bone of the upper tibia is recommended (the fibula being divided in its mid-shaft). This unites quickly and plaster immobilization is only needed for eight to ten weeks.

Mr. E. A. NICOLL read a paper entitled **The Treatment of Intracapsular Fractures of the Neck of the Femur.**

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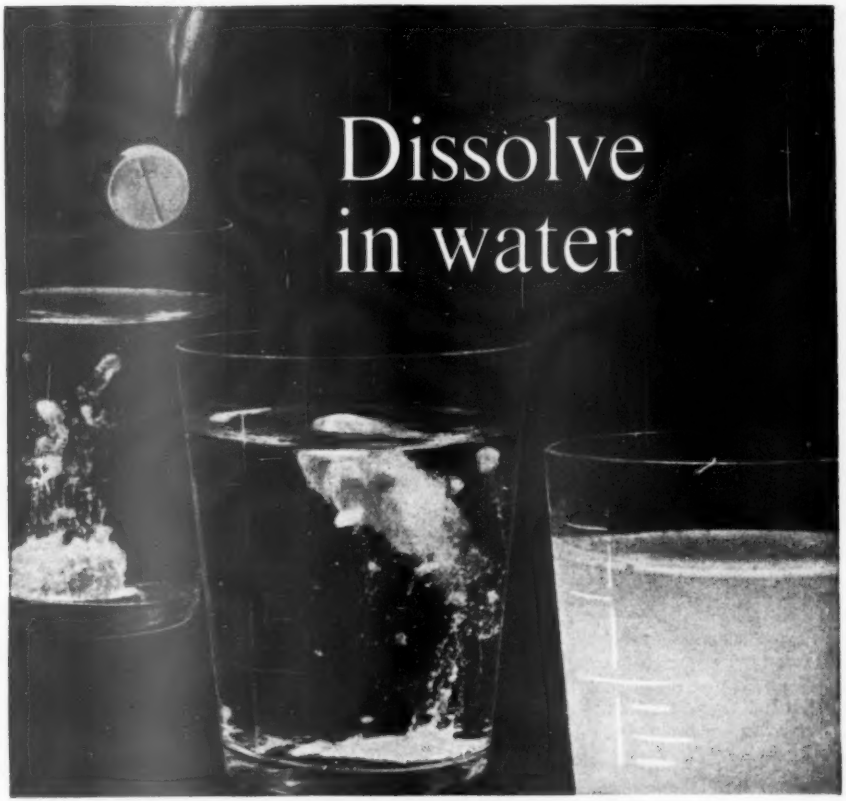

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BOOK REVIEWS

The Rewards of Medicine, and Other Essays. By Hugh Barber, F.R.C.P. (Pp. 140. 15s.) London: H. K. Lewis & Co. Ltd. 1959.

Nearly all these essays have been published during the last decade in the *Guy's Hospital Gazette* or in the *Practitioner*, but we are glad to see them reproduced in a single volume of convenient size.

There are times when the busiest practitioner needs some relaxation, and if he can find this in literature so much the better for him. We commend Dr. Barber's essays and congratulate him on the combination of wide knowledge, practical wisdom, humour, and sense of proportion which they display. They deal with almost every variety of human activity which may come within the doctor's experience. Dr. Barber has the happy knack of being able to write in a light and even humorous vein on really serious questions, but in all the essays his underlying serious and sympathetic understanding is apparent. In an age in which there is so much heavy reading this book comes like a welcome draught of spring water to one who has been pursuing his way through hot and arid plains.

Physiology of the Retina and Visual Pathway. By G. S. Brindley, M.A., M.D. (Pp. xi+298; illustrated. 35s.) London: Edward Arnold (Publishers) Ltd. 1960.

The first half of this book (Chapters I–III) is concerned with the objective data of the retina and the visual pathways, as provided by biochemical, electrophysiological and anatomical studies. The other half (Chapters IV–VII) considers the results of sensory experiments, i.e. those in which the data have been obtained by the mediation of a human subject. The two halves are well integrated by the theme "How does the human visual pathway work?"

The book is a valuable addition to the literature of the subject, not only because of the mass of original work consulted and quoted, but also because the author's strongly logical approach has knit the whole together into a continuous narrative.

The work appears almost free from errors and only one misleading passage was noted by the reviewer. This (a statement on p. 9 that there is a striking difference in behaviour between metarhodopsin and transient orange) arises through the author's acceptance of a conclusion in the literature at its face value when, in the light of subsequent knowledge, it is evident that the original conclusion was invalid. Thus although Lythgoe and Quilliam believed that transient orange (when allowed to stand in darkness at 3° C) was wholly converted into indicator yellow it is apparent that their final absorption curve, though labelled "I.Y." (Fig. 1.1, p. 6), is not due to indicator yellow alone. Unfortunately Lythgoe and Quilliam did not re-expose their solution to light to ascertain whether or not any photolabile material was present. However, there can be little doubt from the form of the final absorption curve "I.Y." that regenerated pigment as well as indicator yellow was produced from the transient orange, just as is the case when metarhodopsin is allowed to stand in darkness.

In his preface the author states "This is a tightly written book". In the reviewer's opinion it could, with a little more effort, have been made easier to read.

These criticisms, however, are minor ones; the author deserves thanks for having produced a well-reasoned and balanced account of the subject. It will be of especial value to the research worker, but advanced students will also derive profit from a careful study of its pages.

Principles of Human Pathology. By Edward B. Smith, M.D., Parker R. Beamer, Ph.D., M.D., Frank Vellios, M.D., and Dale M. Schulz, M.S., M.D. (Pp. xi+1123; illustrated. 95s.) London: Oxford University Press. 1959.

In this book the authors have broken away from the conventional pattern of the older textbooks of pathology, and there is a commendable attempt to correlate tissue changes with disturbances of physiology, morbid anatomy being blended with a judicious mixture of bacteriology, hæmatology and chemical pathology.

It is made clear on the dust-cover that the main emphasis is not on morbid anatomy. This is fortunate, since otherwise it would be difficult to excuse the poor quality of the illustrations. Many of the photographs are muddy and uninformative (e.g. hepatic metastases, p. 846), and far too many of the photomicrographs look simply out of focus.

The British student will find the distinction between "adeno-carcinoma" and "columnar-cell carcinoma" confusing, and the use of the term "carcinoma simplex" as a naked-eye description, rather than as a microscopic one, will be equally unfamiliar. His teacher may wonder why, in a 13-page chapter on tumours, the authors make room for such rarities as the hibernoma, dermatofibrosarcoma protuberans, juvenile nasopharyngeal fibroma, sarcoma botryoides, hæmangiopericytoma, chemodectoma and mesenchymoma.

He may also ask why more space is devoted to Gaucher's than to Hodgkin's disease.

On the credit side, the sections on vascular and renal disease are clearly written; there are admirable essays on allergy and infection; and the presentation of contemporary problems, such as the pathology of irradiation and iatrogenic disease, is well done.

This is a book that will satisfy neither student nor specialist; neither morbid anatomist nor bacteriologist; neither chemist nor hæmatologist. Because it has something for everybody, it has not enough for anybody.

Principles of Bone X-ray Diagnosis. By George Simon, M.D., M.R.C.P., F.F.R. (Pp. xxi+170+8; illustrated. 57s. 6d.) London: Butterworth & Co. (Publishers) Ltd. 1960.

In this book the author adopts the same pattern as in his previous publication on "Principles of X-ray Chest Diagnosis". The material is arranged primarily under the headings of X-ray appearances, the clinical and pathological diagnoses are then deduced from these appearances and an attempt is made to analyse the differential diagnosis. By this rather unorthodox approach the author has provided the reader with a most valuable diagnostic atlas of bone disease, giving a fundamental approach to the interpretation of the X-ray films rather than an orthodox textbook description. This is of particular value for the more advanced students who have already acquired some knowledge of basic radiology of bone diseases. With well-chosen and beautifully reproduced illustrations the salient patterns of the various lesions are made quite clear and the analysis of the differential diagnosis can easily be followed.

Some hints on techniques are most valuable and so are the pathological tables on classification of bone tumours and biochemical data in the appendix. This book is highly recommended, not only to senior students, but also to the practising radiologist.

Forensic Medicine: Observation and Interpretation. By A. Keith Mant, M.D.(Lond.). (Pp. vii+262; illustrated. 42s.) London: Lloyd-Luke (Medical Books) Ltd. 1959.

This small book, stressing the importance of observation at the scene of crime, will be a valuable addition to most standard textbooks from the point of view of approach to cases of sudden death. From this aspect, it will obviously be an asset to police surgeons and general practitioners by its more detailed treatment; at the same time, it contains little fresh or original material. Nevertheless, it undoubtedly strives to educate practitioners in the proper approach to a case. It may also be of value to those investigating officers who can absorb the technical aspects as well as to those who advise them. It can be heartily recommended to anyone in general practice although a strange omission is alcoholic intoxication. One criticism of the many excellent photographs is that the victims can be recognized. Most of those portions which are based entirely upon the author's personal experience are a most valuable record and the book should certainly be easily available for reference, but as a textbook it has shortcomings.

The Placenta and Fetal Membranes. Edited by Claude A. Villee, Ph.D. (Pp. x+404; illustrated. 80s.) Baltimore: The Williams & Wilkins Company. London: Baillière, Tindall & Cox Ltd. 1960.

This report of a conference on the placenta held at Princeton, N.J., in November 1958 contains no original contribution; there are eight concise reviews by well-known workers, some 2,700 references have been collected and are each given with a short summary of the salient features of the publications.

It is unlikely that the reviews will be of much value to other workers in the same fields because of their brevity. For example, the whole subject of transmission of antibodies from mother to fœtus is dealt with in eleven pages, albeit very pleasantly written, and biochemical aspects written by the editor occupy only seven pages.

These reviews may have great interest, however, to those unacquainted with the particular subject, and the book is well printed and easy to read.

Infectious Diseases of Animals. Diseases Due to Bacteria. In two volumes. Edited by A. W. Stableforth, D.Sc., M.R.C.V.S., D.V.S.M., and I. A. Galloway, D.Sc., M.R.C.V.S. (Pp. x+810; illustrated. 160s.) London: Butterworths Scientific Publications. 1959.

The editors have succeeded in supplying a critical and adequately referenced account of the important bacterial and fungal diseases of domesticated animals. There is an alphabetical order and Vol. 1 covers those infections from actinomycosis to listeriosis and includes the fungal and leptospiral diseases. Vol. 2 ranges from necrobacillosis to vibriosis and takes in the pleuro-pneumonia group of diseases. Most of the authors are of senior rank and experts in their particular sphere; all are from the United Kingdom or the Commonwealth.

Some of the chapters, such as that on brucellosis, are long and detailed; others, for example that on coliform infections, are short yet interesting and informative. A few contain too much detail for those who have insufficient background

to appreciate the main story. So much attention is paid to the types, the groups, the antigens and the classification of salmonella and of streptococci, that there is a danger of dullness and of obscuring matters of interest and importance.

These are minor criticisms. The two volumes could well be consulted by those with some general bacteriological knowledge but with little training in veterinary pathology; they should be used extensively by those who have had a veterinary training for herein lies an immense amount of well-documented information.

Communicable and Infectious Diseases. Diagnosis, Prevention, Treatment. By Franklin H. Top, A.B., M.D., M.P.H., F.A.C.P., F.A.A.P., F.A.P.H.A. 4th ed. (Pp. 812; illustrated. 150s.) St. Louis: The C.V. Mosby Company. London: Henry Kimpton. 1960.

The fourth edition of Top's well-known book is enriched with three new chapters—on acute respiratory infections, enteroviruses and staphylococcal infections—and maintains its high standard, covering the whole field of communicable diseases seen in temperate regions. The introductory section on general principles includes an admirable section on chemotherapeutic agents which provides in tabular form a guide to the differing sensitivities of the various microbial species and their liability to develop resistance, with indications of the appropriate dosage and the toxic side effects of the drugs.

The diseases are grouped under the portals of entry of the microbes and each chapter summarizes the history, epidemiology, ætiology and clinical features of the infection. Treatment and prevention are also discussed, usually in a very practical fashion. Each chapter is provided with a good list of up-to-date references. As is to be expected in a compilation by many authors, the chapters are not all of equal value, but the book can be thoroughly recommended as a textbook of the communicable diseases.

Diseases of the Nervous System. Described for Practitioners and Students. By Sir Francis Walshe, M.D., D.Sc., F.R.S. 9th ed. (Pp. xvi+373; illustrated. 30s.) Edinburgh and London: E. & S. Livingstone Ltd. 1958.

This book remains one of the most readable of medical textbooks. The two chapters by Dr. J. M. Walshe are welcome and clearly present some of the recent additions to our knowledge of nervous disorders (hepatic coma and hepatolenticular degeneration). The latest concepts of cerebrovascular disorders are discussed and the importance of obstruction of the carotid and basilar arteries is adequately dealt with. There is much good advice for the doctor in the wise management of nervous diseases, and the warnings against over-zealous and officious interference in the patient's life and future are particularly important. The author intends to supply the needs of the student and the general practitioner and he is successful, but it is a pity that a short and well-selected bibliography has not been included. The student, stimulated by the author's presentation, might well be encouraged to refer to the original literature, and the value of the book for the practitioner would be enhanced. There are some points on which one must be critical. The description of the fibres in the chiasm (p. 41) is not clear. The fibres from the "nasal half field" are said to cross; this could well refer to the visual field and not to the retinal field, which is presumably the author's intention. Hormonal treatment *is* successful in hypopituitarism (p. 90), and most observers would regard the presence of the jaw jerk as normal (p. 243). There is no reference to temporal arteritis as a cause of headache.

The Purpose and Practice of Medicine. Selections from the Writings of Sir James Spence. With a memoir by Sir John Charles. (Pp. x+308. 42s.) London: Oxford University Press (for the University of Durham). 1960.

Sir James Spence, who died in 1954, was the first whole-time Professor of Child Health in Great Britain and, at the same time, one of the first to demonstrate that the practice of pædiatrics must extend outside the hospital and embrace the home. He left behind him a Department in which the tradition of social investigation and family study enlivened both the practice and the teaching of medicine. In this volume his friends and colleagues present a selection of his writings and Sir John Charles has contributed a fascinating and delightful memoir. It is perhaps a pity that the book contains no portrait, yet, as we read his biography and follow the development of his philosophy from his writings, he stands before us as a great humanist and a great physician. This book will be warmly welcomed by all who knew him and will be widely read by the many, throughout the world, who have been influenced by his work.

Modern Nutrition in Health and Disease. Dietotherapy. Edited by Michael G. Wohl, M.D., and Robert S. Goodhart, M.D. 2nd ed. (Pp. 1152; illustrated. 138s.) London: Henry Kimpton. 1960.

This large volume is the second edition of a book which first appeared in the U.S.A. in 1955 as a sequel to a previous book by the senior author called "Dietotherapy". It is a compilation of review articles by 59 authors, all of whom

(apart from one Mexican) reside in the U.S.A. It is an impressive mine of information and contains some valuable and authoritative papers.

The book is divided into three parts. The first is entitled "Normal Nutrition", though it deals with such subjects as laboratory aids in diagnosis of malnutrition. The second is concerned with "Nutrition in Disease", while a short third section deals with "Nutrition in Periods of Physiologic Stress"; this includes a synopsis of the current recommendations on nutrition of the (U.S.) Office of Civil Defence Mobilisation. All the chapters have extensive bibliographies referring chiefly to the American literature.

It seems unlikely that this book will be in much demand outside North America; for one thing the price is prohibitive for most doctors, dietitians and medical students. But it is recommended as a useful reference book for medical libraries.

Florence Nightingale's Nurses. By Lucy Seymer. (Pp. xi+169; illustrated. 20s.) London: Pitman Medical Publishing Co. Ltd. 1960.

This story of the foundation and development of the renowned Nightingale School of Nursing at St. Thomas's Hospital should be read by everyone interested in the history of nursing. Written by one who was trained in the School, it describes how early difficulties were overcome, how the new discipline spread first over the British Isles and then throughout the English-speaking world, and how, after a brief period of reaction, the mother-school again took the lead in advancing the cause of nursing. The story needed telling and it is appropriate that this most interesting account should appear in the centenary year of the School's foundation.

Miss Nightingale is shown in a new light and the excellent work done by Mrs. Wardroper, Miss Crossland, Dame Alicia Lloyd-Still and many others is clearly indicated. Yet how strange that the controlling Council of the School should have been, apart from Miss Nightingale herself, composed entirely of men!

This is a book to read and think over, rather than to talk about. No subscription raised in honour of any person has ever been so fruitful in benevolent results to the human race as that subscribed in honour of Florence Nightingale.

Pathology of Infancy and Childhood. By Agnes R. Macgregor, M.D., F.R.C.P.E., F.R.C.O.G. (Pp. viii+631; illustrated. 75s.) Edinburgh and London: E. & S. Livingstone Ltd. 1960.

It is fitting that one of the first textbooks on pædiatric pathology should be written by Dr. Agnes Macgregor whose experience in this field is well recognized. The first section of the book gives a concise account of the pathology of the placenta, fœtus and newborn infant, while the second deals with congenital malformations. Together these comprise about one-third of the whole book. Other sections contain descriptions of the lesions found in infective diseases, the "collagen group" of disorders, diseases of metabolism and of the blood and neoplastic diseases. The last section is concerned with a miscellaneous group including disorders of the skin and central nervous system and a useful short note on sudden death. The appendix on post-mortem technique for the fœtus and the tables of weights and measurements will prove helpful. The wide range of subjects covered has unfortunately led to some conditions receiving less consideration than they merit. The bibliography is brief and largely confined to a few standard references. The production is of a high order. The colour and monochrome photomicrographs are well chosen and beautifully reproduced. The book will prove valuable to pædiatrician and pædiatric pathologist.

Selected Papers. By Sir Geoffrey Jefferson. (Pp. xi+563; illustrated. £5 5s.) London: Pitman Medical Publishing Co. Ltd. 1960.

Reading any of Sir Geoffrey Jefferson's work is as entertaining as it is instructive and this collection of some of his important papers makes a delightful volume. It is made up of four parts, Reflections, Portraits, Neurosurgery and a short "Envoi". The historical papers are all well worth reading, and his essays on Harvey Cushing are specially delightful. There is another on three Manchester "Pioneers in Neurology", James Ross, William Thorburn and R. T. Williamson, and studies of Macewen, Horsley and Marshall Hall. The collection of clinical papers numbers fourteen, among which are his important contributions on intracranial aneurysms, extrasellar extensions of pituitary tumours and trigeminal neurinomas. For these clinical papers alone this volume will be valuable to those neurologists and neurosurgeons whose libraries do not extend back twenty years and more. In the last section there are two chapters. One is an account of a visit to Russia in 1956 and recollections of his earlier stay there in 1917. Then he had what he describes as a "front-window" view of the Revolution and at the Anglo-Russian Hospital operated on some of the first casualties. The last chapter he calls "On Being Happy and Liking It". His own great source of happiness has been his work, and his bounding enthusiasm for it shines very clearly through all his writing. The book is well produced and by present standards not excessively expensive.

Growing up in Newcastle upon Tyne. By F. J. W. Miller, S. D. M. Court, W. S. Walton, and E. G. Knox. (Pp. xxi+369; illustrated. 25s.) London: Oxford University Press (for the Nuffield Foundation). 1960.

There can be few individuals concerned with the health and welfare of children who to-day are unaware of the Tyneside Thousand Family Survey, as the investigation has come to be known The primary purpose of this clinical and epidemiological study, started in 1947 and still continuing, was to reveal the pattern and extent of disease in Newcastle children, particularly the origins and associations of ill-health and abnormality in the young. Hitherto, concepts of child health, upon which undergraduate teaching and preventive pædiatrics must be based, have stemmed largely from hospital experience. The first report which appeared six years ago dealt with the first year of life and gave the facts of development and disease concerning a representative sample of the city's infants; this book was widely acclaimed. The second volume just published dealing with the same survey-group and covering now the pre-school period is an equally outstanding medical and social document which deserves the attention of all those who in different ways care for children, whether doctors or not.

The project has throughout remained a joint undertaking shared between the Nuffield Department of Child Health, King's College, and the City Health Department, Newcastle. Everyone concerned in this fruitful partnership must be congratulated. The investigation will continue until 1962 by which time the children will have reached school-leaving age. All who have followed this fascinating longitudinal study will now eagerly look forward to reading the third and final volume.

Fellowship of Surgeons. A History of the American College of Surgeons. By Loyal Davis, M.D., F.A.C.S. (Pp. vi+523. 84s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1960.

This history of the American College of Surgeons makes interesting but in some places surprising reading. The hero of the story is Dr. Franklin H. Martin (1857–1935) who was the leading spirit in the foundation of the journal *Surgery, Gynecology and Obstetrics*, of the Clinical Congress of Surgery, and of the American College of Surgeons. He was a man of dynamic personality who faced difficulties only to overcome them.

There is no doubt that the American College has greatly helped to raise the standard of surgery and to elevate the ethics of surgeons in the United States; it has also been a pioneer in the inspection of hospitals so that a high level of surgery may be performed in them. It has never been an examining body and differs greatly from the English College in its administrative procedures. When, however, the author states that the story of the College is that of the development and progress of surgery in America he might with justice add the word "recent", for there was much good surgery in America before 1913. The author makes many critical comments which throw light on the rivalries, suspicions and jealousies inseparable from the politics of public institutions. Sometimes the wealth of detail hides the story and there are no illustrations to give relief, but the book is a valuable contribution to the history of surgery.

Biological Problems of Grafting. A Symposium. Liège University. Edited by F. Albert and P. B. Medawar. (Pp. xii+453; illustrated. 50s.) Oxford: Blackwell Scientific Publications. 1959.

The biological problems which are faced in this book are among the most fascinating of our century, and the editors are indeed to be congratulated for a presentation which conveys with clarity and freshness the discussions of this conference at Liège. For this is an intimate account of a group of biologists exploring the basic levels of a subject which, besides providing results which are of interest to all concerned in the practice of tissue grafting, offers numerous concepts of cell behaviour of wide significance for human pathology.

The surging enthusiasm for transplantation studies has latterly resulted in a crop of conferences bulging with the hastily conceived contributions of those who have recently mounted this bandwaggon. On the other hand the thirty papers of this volume are distinguished as mature products of experienced and pioneer workers in this field.

Here are provided models for the way in which the immune process can evoke disease and death by the graft-versus-host reaction which presumably forms the basis of the so-called runt or homologous disease; explorations of possible approaches to the therapy of neoplastic disease involving methods for inducing tolerance of grafts; and extensive experimental data on the grafting of bone marrow and reticulo-endothelial cells, the understanding of which should help to limit the iatrogenic diseases of transplantation in man.

All those interested in the immunological approach to the problems of human pathogenesis and therapy by grafting will find interest in this stimulating book.

Studies on Vertebrate Neurogenesis. By S. Ramón y Cajal. Translated by Lloyd Guth, M.D. (Pp. xiv+432; illustrated. £5 8s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1960.

In 1928 there appeared an English edition of Cajal's "Degeneration and regeneration of the nervous system" which was fascinating both for the knowledge it contained and for the clarity of the writing and the illustrations.

In 1929 a group of scientists from Montevideo published, in French, a collection of Cajal's articles upon the histogenesis of the vertebrate central and peripheral nervous system. Most of the articles had been originally published at the end of the last century or at the beginning of this century, in Spanish. The French edition has now been translated into English by Lloyd Guth of Bethesda and a bibliography has been added. Here again, there is the clarity of expression and illustration of which Cajal was such a master.

Most of what he describes has passed into the general body of knowledge and the interpretation of his facts may have altered in the light of other advances, but there are many advantages in having gathered together in one volume many of the original articles upon which our knowledge is based.

For neurologists, embryologists and biologists this book is of considerable value. The publishers are to be congratulated on the format of the book but the price is high.

Atlas and Manual of Dermatology and Venereology. By Professor Dr. W. Burckhardt. Translated and edited by Stephen Epstein, M.D. (Pp. xiii+276; 99 colour plates and 73 black and white illustrations. 112s.) London: Baillière, Tindall and Cox: 1959.

This book is the American edition of a Swiss publication and has been translated by the second author. It is designed for general practitioners, medical students and non-dermatological specialists.

Those who are familiar with Geigy's "Folia Dermatologica" will recognize the illustrations. With few exceptions the colour photographs are excellent and monochrome reproductions are equally helpful. Descriptions of diseases are clear and one can find few faults in these or in the treatment methods suggested. Some of the simpler remedies will be unfamiliar to English readers but if the reader is prepared to substitute the standard preparations of the British National Formulary he will not find this a serious fault. It is noted that benzyl benzoate is not mentioned in the treatment of scabies although this is still the accepted treatment in this country. One finds it strange also to read that in molluscum contagiosum the lesions are located on the face, genital area and hands, rarely on the trunk.

This book must be considered a useful addition to the shorter texts on dermatology. The section devoted to venereal diseases is short but adequate.

The Human Apocrine Sweat Gland in Health and Disease. By Harry J. Hurley, M.D., D.Sc. (Med.), and Walter B. Shelley, M.D., Ph.D. (American Lecture Series No. 376. Pp. x+138; illustrated. 52s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1960.

The work of Shelley and his colleagues on the apocrine sweat glands is well known and has appeared in numerous articles during the past few years. This book by the two main participants in this research is not a collection of these articles but rather a full account of the work and a review of existing knowledge concerning the apocrine glands as seen in man and some other mammals. It may come as a surprise to many to learn that the apocrine glands individually are about ten times the size of eccrine sweat glands and are larger than sebaceous glands. If the skin is reflected in suitable sites they become visible to the naked eye.

The apocrine glands are responsible for the characteristic body odour of man, not on account of the secretion itself which is opalescent but practically odourless but on account of bacterial action which brings about its decomposition. Aluminium chloride owes its value as a deodorant to its bacteriocidal properties and also apparently to a direct chemical action which neutralizes the odour after it has been produced. It in no way reduces the quantity of apocrine sweat secreted.

This book is well produced and most of the illustrations are excellent. A few minor printing errors should be corrected in later editions. It is a first rate monograph and should become the standard work of reference in this subject.

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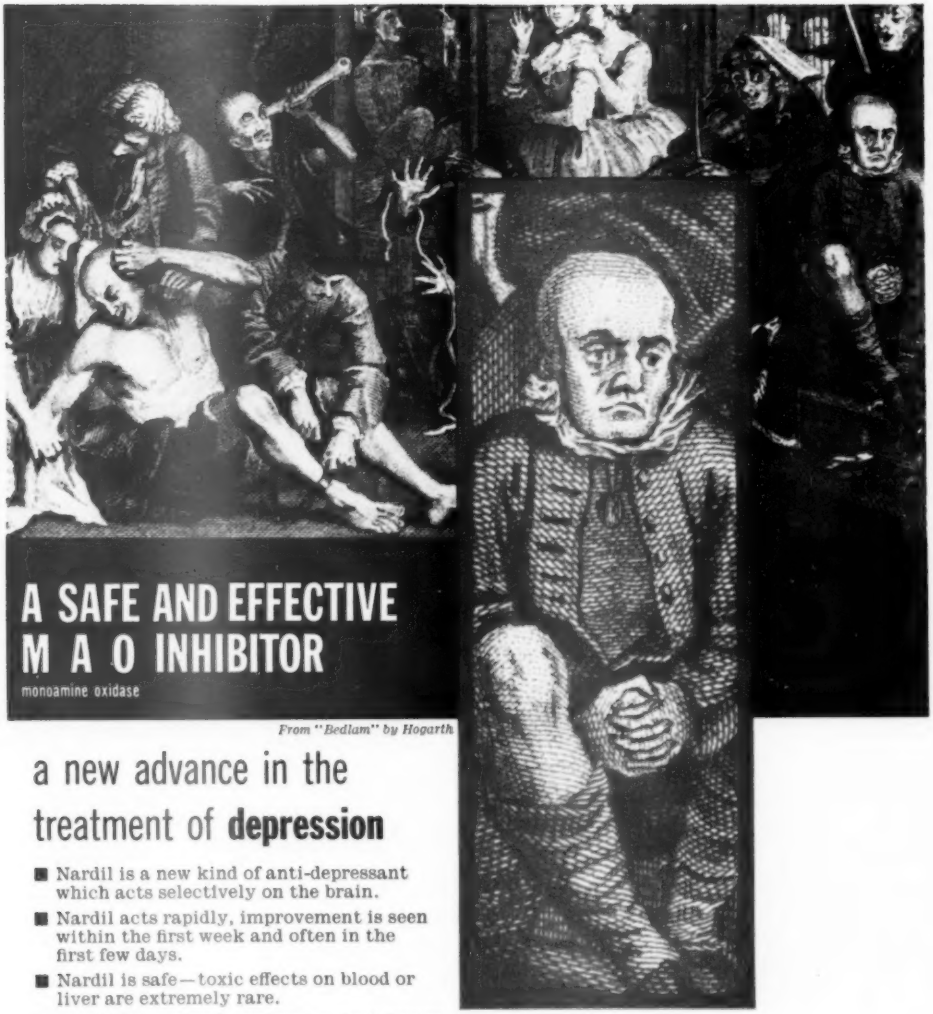

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